BCT is generally associated with fewer complications, similar QoL, and lower resource use, leading to superior cost-effectiveness compared to mastectomy followed by BR.

Casimir Kouwenberg

Psychological Impact and Cost-Effectiveness of Breast Cancer Surgery

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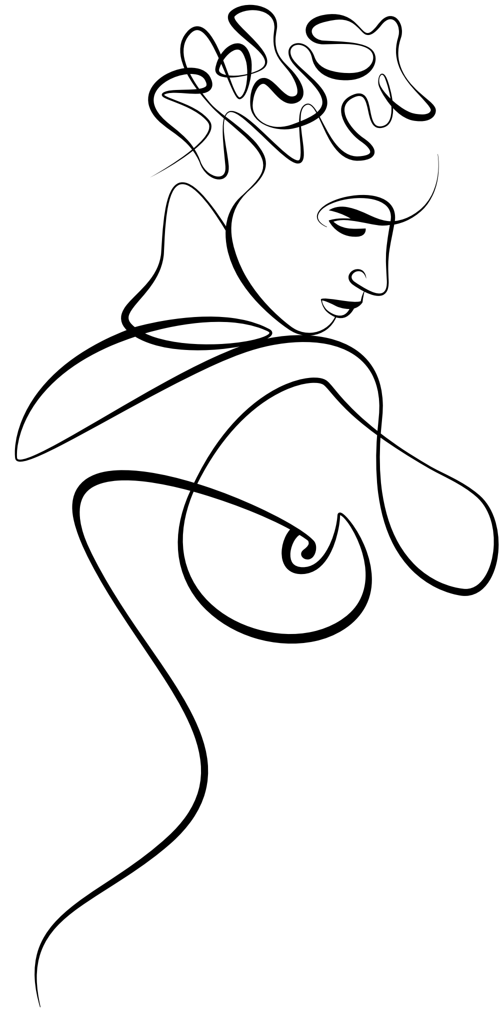

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ISBN: 978-94-6416-306-3
Design: Peter Duifhuizen (Sneldruk & Ontwerp)
Print: Ridderprint | www.ridderprint.nl

The research leading to this thesis was financially supported by the Esser stichting and the department of Plastic and Reconstructive Surgery and the department of Psychiatry section Medical Psychology and Psychotherapy.

Psychological Impact and Cost-Effectiveness of Breast Cancer Surgery

Psychologische impact en kosteneffectiviteit van borstkanker chirurgie

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof.dr. R.C.M.E. Engels

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

Woensdag 16 december 2020 om 11:30 uur

door

Kouwenberg, Casimir Alexis Eloi
geboren te Hilversum

Erasmus University Rotterdam

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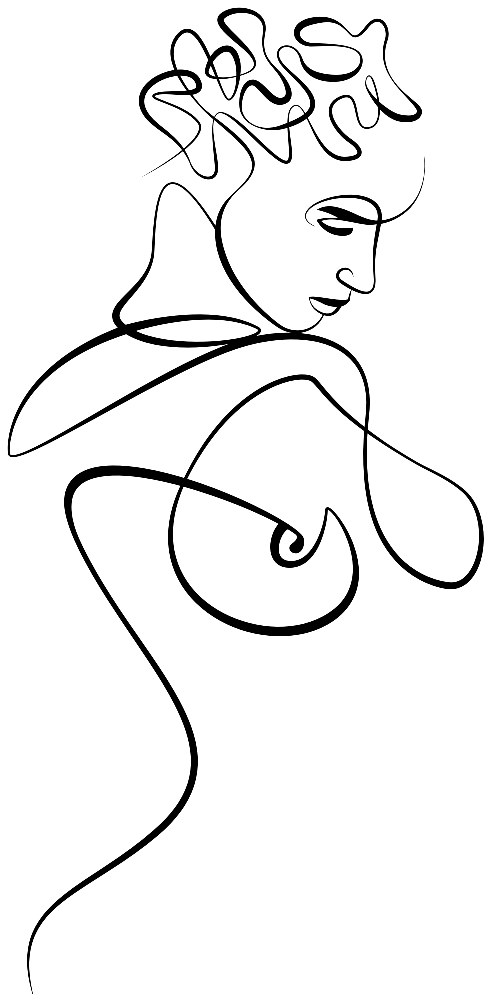

Chapter **1**

General introduction

Introduction

Breast cancer is the most common type of cancer in women in the Netherlands, with a lifetime risk of 1 out of 8 and about 17,000 new cases annually.[1] Immediately after receiving the diagnosis breast cancer, a patient needs to decide together with her surgeon, which type of surgical treatment is optimal. The first decision is between mastectomy or breast conserving surgery followed by radiation therapy (breast conserving therapy, BCT). If the patient and her surgeon opt for mastectomy, the patient is presented with an additional set of choices, namely whether she wants her breast to be reconstructed and if so, how. These choices lead to a multitude of possible treatment pathways to choose from. Currently, the impact of a choice for one of these pathways on the treatment burden, health-related quality of life outcomes and healthcare resource use is unclear, due to limited and often conflicting evidence presented in the literature. This complicates the decision-making process for both patient and surgeon.

The current PhD-project aimed to reduce this uncertainty by making innovative use of the state-of-the-art healthcare registrations that are currently in place in the Netherlands. These registrations allow extensive information to be gathered on the complete breast cancer related healthcare use of a large cohort of patients and combine it with comprehensive, national patient and cancer treatment databases, such as the National Cancer Registry (NCR). These registration systems were additionally used to identify and approach breast cancer patients to investigate the long-term health-related quality of life after four common surgical treatment options for breast cancer and the effect of complications.

Methods of postmastectomy breast reconstruction

If a mastectomy has to be performed, the patient may decide she wants her breast to be reconstructed. In general, there are two main types of breast reconstruction (BR): either using implants or autologous tissue. Each of these BR types have advantages and disadvantages which are discussed in the following paragraphs. The reconstruction of the breast is often followed by additional operations to improve symmetry or treat complications, followed by nipple reconstruction and tattooing of the areola.[2]

Implant-based breast reconstruction

With the introduction of silicone breast implants in 1964, the era of modern BR began. In the decades following, the quality of implants has improved, and implant-based BR is widely used. BR by using implants is a relatively straightforward procedure with reduced operative time, a relatively short postoperative recovery and a lack of donor-site morbidity. Implant-based techniques can therefore be performed in basically all hospitals treating breast cancer patients.

Implant-BR may be performed either as a one-stage (direct insertion of a definite prosthesis) or as a two-stage procedure (insertion of a tissue expander followed by replacement with a definite implant during a second procedure). However, a one-stage reconstruction may not be feasible in all patients and is generally recommended only in specific situations. Frequently, it is necessary to stretch the deficient local skin and muscles using a tissue expander (silicone balloon) to create adequate soft tissue coverage of the breast implant. Postoperatively, the tissue expander (TE) is gradually inflated using injections with saline during weekly visits to the outpatient clinic.

An important disadvantage of implants inserted in the human body is the formation of a surrounding capsule of scar tissue, which is a natural response (foreign body reaction) and is a frequent reason for implant removal or replacement. This capsule may contract over time, which tightens and squeezes the implant (capsular contracture). Besides physical complaints such as pain and discomfort, capsular contracture also can cause a distortion of the appearance of the breast, thereby negatively affecting the aesthetic result. Implant rupture is another frequent reason for implant removal or replacement. Approximately 50% of all women who have opted for breast reconstruction using implants require reoperation in the long-term.[3]

In the last couple of years, an increasing number of reports have shown a considerably larger risk of the development of a rare and potentially lethal anaplastic large cell lymphoma (BIA-ALCL) after implant-BR than was previously assumed.[4] This finding has been widely picked-up by the media and has led to a ban for certain breast implant types in some countries over the world. It has also led to fear and many questions among patients that previously have undergone implant-BR as well as patients that have to decide on the type of BR.

Autologous breast reconstruction

A breast mound may also be reconstructed using autologous tissue only. Excess skin and fat with or without the underlying muscle from basically anywhere in the body can theoretically be used. However, usually abdominal tissue is used because of its availability and relatively low donor-site morbidity. The Transverse Rectus Abdominis Myocutaneous (TRAM) flap includes skin, fat and muscle from the lower abdomen which is transferred to the chest wall.[5] It can either be used as a pedicled (where the bloodvessels remain connected to their origin) or free flap (where the bloodvessels are reattached to a bloodvessel in another location) requiring a smaller proportion of the abdominal muscle. Currently, the most popular autologous method is the Deep Inferior Epigastric artery Perforator (DIEP) flap, also using abdominal fat and skin, but leaving the abdominal muscles intact, which reduces the chance of abdominal muscle weakness or hernia formation.[6]

At the Erasmus MC in Rotterdam, this latter technique has been performed since 2001. Advantages of this BR procedure are: there is no need for foreign material to reconstruct a breast; damage to the abdominal wall is minimized compared to pedicled or free TRAM flap techniques; and the reconstructed breast is similar to a natural breast that feels warm, is soft with a natural appearance and adjusts to body weight fluctuations.[6] However, compared to implant techniques, the DIEP-flap technique takes profoundly longer in terms of operative time and recovery. In addition, a large abdominal donor-site wound bed is created after harvesting tissue that is needed for reconstruction which may lead to donor-site morbidity.

Evaluating patient-reported outcomes: PROMs and HRQoL

In recent years large changes have emerged in how healthcare interventions are evaluated. Most notable are the introduction of Patient-Reported Outcome Measures (PROMs) and the concept of value-based healthcare which states that providing high value for patients should become the overarching goal of healthcare delivery.[7] The patient has become the center of attention using PROMs to assess the impact of their disease and treatment on their quality of life, which is becoming the new benchmark to which treatments must measure up. Ideally, value to the patient should guide performance improvement in healthcare. Rigorous, disciplined measurement and improvement of this value would be the best way to drive system progress.[7, 8]

Research has shown that Health-Related Quality of Life (HRQoL) is relatively high in breast cancer patients following treatment compared to other types of cancer, but evidence about possible differences in HRQoL after different treatment options is conflicting.[9-12] For instance, there are both studies that did and did not find differences in HRQoL between patients who had undergone BCT or mastectomy.[13] Also, several higher quality studies did not find statistically significant differences in HRQoL, body image, and sexuality between patients with or without BR.[14] This conflicting evidence may be explained by variation in the use of PROMs, study designs, and patient populations. The impact of different surgical breast cancer treatment possibilities on HRQoL is in need of a reexamination, because valid information about the outcome of treatment options is vital for informed clinical decision-making and healthcare policy makers.

Until now, outcomes have been generally measured in small, cross-sectional, mono-center studies, which can explain the conflicting evidence found. Ideally, one would have to include all surgical options relevant to breast cancer patients in one large prospective cohort study.[14] Santosa et al. performed such a large prospective study, which compared patients with implant-BR and autologous-BR two years after their surgery.[15] They found that autologous-BR patients were generally more satisfied with their breasts and had better psychosocial and sexual well-being as measured with the Breast-Q. Furthermore, outcomes measured over a longer period of time would be of interest, as different surgical outcomes may have a different HRQoL-course over time. For example, recovery from surgical complications takes additional time with at least a temporary negative effect on HRQoL.[16, 17]

Unfortunately, BR has a relatively high risk of postoperative complications that can sometimes even result in the complete loss of the reconstructed breast (BR-failure). A recent large, prospective study reported BR overall complication rates of 26.6-31.3% for implant-BR and 35.8-47.4% for autologous-BR techniques with BR-failure rates of 7.1% and 1.3-2.1% respectively.[18]

Few studies have investigated the potential negative psychological consequences of a BR-failure. One recent qualitative study showed that an autologous-BR failure has a large emotional impact on patients.[19] Quantitative studies by our research group have shown that postoperative complications (including BR-failures) were associated with substantial psychological distress in the short-term, but that in the long-term these levels of distress returned to values comparable to that of patients without such postoperative complications.[16, 20] However, quantitative studies provide only limited insight into which experiences lead to distress in patients confronted with a BR-failure. Qualitative studies that investigated the effect of an implant-based BR-failure on patients' quality of life can provide more information but are lacking so far. In addition, plastic surgeons who perform the procedure may also be affected by the event of a BR-failure. Several studies have shown that the occurrence of serious adverse events may have a strong impact on the healthcare provider involved, also referred to as the "second victim" phenomenon.[21, 22]

Evaluating health economic outcomes: QALYs and CUA

The formal way of evaluating the value of a healthcare intervention is by performing a cost-effectiveness analysis (CEA). Strictly speaking, in this kind of analysis any effectiveness measure could be used, however, through the years the norm has become to use the "quality adjusted life year" (QALY) as the effect measure. The reasoning for the use QALY's is that interventions in healthcare can have an effect on two outcomes: survival and quality of life. Both are important to consider in economic evaluations of healthcare interventions and both can be used to justify costs. Analyses that use QALYs as the effect measure are formally called cost-utility analysis (CUA), however, they are still more frequently referred to as CEA.

Currently, QALYs are most often measured using generic preference-based health status measures (GPBM). Examples of such measures are the EQ-5D, the SF-6D and the HUI3. It has been claimed that these generic health-related quality of life measures can be used for all interventions and patient groups.[23] This generic property is of great value in CUA as the direct comparison of the cost-effectiveness of different interventions is one of the key reasons for performing such an analysis. The questionnaire used in this thesis is the EQ-5D. In the paragraph below this instrument is discussed in more detail.

The EQ-5D is a widely-used generic health-related quality of life (QoL) instrument, designed to measure the most important aspects of health over a broad spectrum of health conditions and diseases.[24] The instrument is specifically used in health economic appraisals where comparisons between very different therapeutic areas/ specialties are made to substantiate the allocation of resources. The EQ-5D was specifically designed to measure the 'Q' in QALY and is notably different from other questionnaires used to measure QoL. It provides 'preference-weighted' quality of life scores (utilities), based on the values that the general public assigns to different health states, which are needed for the calculation of QALYs. An increasing number of reimbursement agencies are requiring a GPBM being the standard outcome measure, with NICE in the UK and ZiNL in the Netherlands requiring the EQ-5D to be used as the effect measure of choice.[25-27] This claim of universal applicability holds true for many conditions, however, for some conditions these GPBMs have been found not to be sensitive enough or to lack relevance.[23] It is unclear whether this is also the case for breast cancer surgery, most notably breast reconstruction interventions, for which the limited attributes included in the instrument may be unsuitable to detect the effects of the intervention on quality of life. It is therefore important to first evaluate whether the EQ-5D is a valid instrument for the evaluation of QoL in BR patients.

Formally evaluating value of breast cancer treatment pathways

Beside the trade-off between risks and benefits for the patient, different treatment pathways have different costs consequences. These differences in costs are relevant, as healthcare budgets are under substantial strain due to the increasing healthcare costs. Society, policy makers and insurance companies are therefore confronted with complex choices about which medical interventions to reimburse. Within such deliberation, the cost-effectiveness of the interventions, is an eminent argument. This is not only relevant when choosing between surgical pathways for breast cancer treatment, but also when the reimbursement of these surgical pathways is in competition with other allocations of the healthcare budget. This is particularly relevant for common surgical treatment pathways for breast cancer such as BR, as these are not life-prolonging. If the outcome of not life-prolonging interventions is measured in QALYs, the outcome can then be compared with life-saving interventions. Evidence that a given surgical treatment has a favorable cost-effectiveness will help to strengthen its position.

Aims and outline of the thesis

The first part addresses the measurement of health-related quality of life in breast cancer patients after breast cancer surgery and breast reconstruction. In Chapter 2 the validity of the EQ-5D for BR following mastectomy for breast cancer was evaluated in a large cohort of patients with a long follow-up. This allowed us to assess whether EQ-5D outcomes were suitable for further use in cost-utility-analyses. In chapter 3 the long-term health-related quality of life after four common surgical treatment options for breast cancer and the effect of complications was retrospectively investigated in 1871 patients. This chapter aimed to compare QoL outcomes of BCT, mastectomy, mastectomy followed by autologous-BR, and mastectomy followed by implant-BR. QoL was assessed using multiple PROMs in a large, multicenter, retrospective, cross-sectional cohort of breast cancer patients up to ten years after diagnosis. Furthermore, the impact of complications on QoL following these different surgical treatment options was also investigated.

The second part of this thesis consists of state-of-the-art cost-effectiveness analysis which aimed to formally compare the value of the four most common breast cancer treatment pathways. In chapter 4, the cost-effectiveness of these pathways was compared. Because the outcomes of the different surgical pathways may be affected by postoperative complications, we also assessed the impact of complications following these four different surgical treatment pathways, on the costs.

The third part of this thesis takes a qualitative approach to evaluate the impact of complications after BR surgery on both the patient and the surgeon. Chapter 5 addresses patients' and surgeons' experiences after failed breast reconstruction, in order to obtain insights that could facilitate improvement in care for both parties.

The final part of this thesis is a general discussion, which entails a chapter based on an opinion article (chapter 6) and a summary (chapter 7). This part of the thesis critically evaluates what the results of this thesis imply for the counseling of breast cancer patients.

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Chapter 2

The validity of the EQ-5D-5L in measuring quality of life benefits of breast reconstruction

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Journal of Plastic, Reconstructive & Aesthetic Surgery. 2019, 72(1):52-61.

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Abstract

Background
The EuroQol EQ-5D-5L instrument is the most widely-used quality of life measure in health economic evaluations. It is unclear whether such a generic instrument is valid enough to estimate the benefits of breast reconstruction (BR), given the specific changes observed in quality of life after BR. Hence, we aimed to evaluate the validity of EQ-5D-5L in patients who had undergone postmastectomy BR.

Methods
In a 10-year cross-sectional cohort study, 463 mastectomy patients completed an online survey: 202 patients with autologous-BR (A-BR), 103 with implant-based-BR (I-BR), and 158 without BR (MAS). The results were used to evaluate the psychometric performance of EQ-5D-5L with respect to the ceiling effect and to known-group, convergent, and discriminant validity, by comparing it with the Breast-Q, the cancer-specific (EORTC-QLQ-C30), and breast cancer-specific (EORTC-QLQ-BR23) questionnaires.

Results
EQ-5D-5L was able to discriminate between patients with and without complications, MAS with or without BR and MAS versus the general population. It was, however, not able to discriminate between *A-BR vs. I-BR as well as BR vs. general population*. It is not clear whether this was due to the insensitivity of the instrument, insufficient sample sizes, or because there were no actual differences in QoL between these groups. Good convergent and discriminant validity of both EQ-5D-5L and its individual dimensions was demonstrated. Additional support for the instrument's validity was revealed by moderate correlations between the generic EQ-5D-5L and specific QoL aspects of BR such as sexuality and body image.

Conclusions
The results of this study support the validity of the EQ-5D-5L as an outcome measure in health economic evaluations of BR.

Introduction

Healthcare budgets are under substantial strain due to increasing healthcare costs. Society and insurance companies are progressively confronted with difficult choices about which medical interventions are to be reimbursed. Because elective procedures such as breast reconstruction (BR) are not life-saving, but primarily aimed at improving quality of life, they may be among the first medical interventions to be critically reviewed. Difficult decisions about which interventions should be reimbursed can only be made when it is possible to reliably compare different medical interventions. The formal way to do this is to perform a cost-effectiveness evaluation that makes use of appropriate measures such as EQ-5D-5L.

EQ-5D-5L is a widely-used generic health-related quality of life (QoL) instrument, designed to measure the most important aspects of health over a broad spectrum of health conditions and diseases.[1] The instrument is especially used in health economic appraisals where comparisons between different therapeutic areas are made when deciding on the allocation of resources. In such comparisons the core value of an intervention for the patients' needs to be evaluated, that is the effect of an intervention both on survival and quality of life. In economic appraisals survival *and* quality of life are combined in the Quality Adjusted Life Year (QALY). QALYs allow, for example, BR to be compared to an intervention in a condition such as diabetes. The QALY is the preferred outcome measure in various guidelines for health economic evaluations from national reimbursement agencies such as NICE in the U.K..[2,3] EQ-5D-5L is specifically designed to measure the Q in QALY and is notably different from other questionnaires employed to measure QoL as it provides 'preference-weighted quality of life scores' (utilities), based on the values of the general public. These utilities are needed for the calculation of QALYs. EQ-5D is the most widely-used questionnaire in health economic evaluations and is the preferred questionnaire of many national reimbursement agencies.[2,4] It is therefore important to evaluate whether EQ-5D-5L is a valid instrument for the evaluation of QoL in BR patients.

Given the requirement to use appropriate and valid QALY estimates and the increased importance of health economic evaluations that provide comparable outcome measures, it is relevant for the field of BR surgery to know whether the generic EQ-5D-5L is a valid instrument to measure the specific benefits of BR. The present study aimed to evaluate the validity of EQ-5D-5L for BR following mastectomy for breast cancer in a large cohort of patients with a long follow-up.

Methods

Patient recruitment

Data were gathered using a cross-sectional online survey sent to patients who in the last 10 years had been treated for breast cancer at Erasmus MC Cancer Institute in Rotterdam, the Netherlands. There were three cohorts of patients who had undergone a mastectomy for breast cancer: autologous BR (A-BR), implant-based BR (I-BR), and women who had not undergone a BR (MAS). Patients were identified using the hospital's reimbursement administrative system with specific codes for the respective procedures. Patients were sent an invitation letter by mail requesting participation in an online survey. Patients not proficient in Dutch or who had developed a distant metastasis were excluded. We considered including patients with a distant metastasis, but a large proportion of this patient group communicated that they did not wish to participate in research on this specific topic. Since inclusion of this sub-population was not necessary with respect to the aim of the study, these patients were excluded on ethical grounds. Respondents filled out an online informed consent form and a series of self-administered questionnaires. Non-responders were contacted three weeks later by telephone and asked to consider participating. The Medical Ethics Committee of the Erasmus MC approved the study (MEC-2015-273).[8]

Measures

EuroQol-5D-5L

EQ-5D-5L is a standardized measure of health status designed to be a simple and generic measure of health-related QoL that can be used in clinical trials and economic evaluations of healthcare interventions.[9] It has a 5-dimension, 5-level descriptive system, covering the dimensions mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. It describes $5^5 = 3125$ unique health states, which all have a utility value known from previous valuation studies. This utility value is anchored at two points, a value of 1.00 indicates the value of 'perfect health' and 0 equals the value of 'death'. In accordance with economic theory and health economic appraisal guidelines, we used the EQ-5D-5L societal utility (value) set specific to the study country, in this case the Netherlands, to score the questionnaire and obtain utility values for our sample.[2,10,11]

Breast-Q

The Breast-Q is a validated patient-reported outcome questionnaire that is widely used in the field of breast surgery.[12] The modules specifically developed for BR and mastectomy were used if applicable. The following five domains of the Breast-Q were used in the current study: 1) physical well-being, 2) psychosocial well-being, 3) sexual well-being, 4) satisfaction with breasts, and 5) satisfaction with the overall outcome. The Breast-Q comes with an official score algorithm in the form of the 'Q-score application'. This application was used to transform the questionnaire responses to the respective modules on a 0 to 100-point scale where a higher score indicates a better outcome on the scales.

EORTC QLQ-C30 and QLQ-BR23

The EORTC questionnaires are measures for evaluating health-related QoL of cancer patients which were designed for use in clinical trials.[13] In the present study, the cancer-specific QLQ-C30 and the breast cancer-specific QLQ-BR23 questionnaires were used. Both have been validated and are widely used in oncology and oncologic surgery patients.[13-15] The EORTC questionnaires consist of various scales where higher scale scores represent higher response levels. This means that a high score on one of the functional or QoL scales represents a high level of functioning or QoL, respectively. In contrast, a high score on one of the symptom scales indicates a high level of problems.[13,15]

Statistical Methods

Characteristics of the study population were analyzed using descriptive statistics. The construct validity of EQ-5D-5L in women who had undergone a postmastectomy BR for breast cancer was evaluated. Construct validity is defined as the degree to which an instrument measures what it was intended to measure.[16] The construct validity of EQ-5D-5L was tested by its correlation with other QoL instruments with known validity for BR and the ability of the EQ-5D-5L to discriminate between various relevant patient groups and outcomes. Three specific forms of construct validity were evaluated.

Distribution of EQ-5D-5L health profiles

The distribution of the responses to the different EQ-5D-5L dimensions and the combination of these responses (the health profiles) within individual patients were assessed. This provides insight into the sensitivity of the instrument in terms of variance in scores on the dimensions and of the number of profiles. It also provides insight about a potential ceiling effect. This ceiling effect refers to the common observation that a high number of patients report 'no problems' on any of the dimensions of EQ-5D. This is often considered a psychometric problem, because it may imply an insufficiently sensitive questionnaire.[16] Hence, we investigated whether BR patients with a perfect health score on EQ-5D-5L also showed very good health scores on the Breast-Q well-being dimensions. To do this, an aggregated mean score of the Breast-Q 'psychosocial', 'chest and upper body' and 'abdomen' well-being scores was calculated for each BR patient.

Known-group validity

The evaluation of known-group validity is based on the idea that distinctively different groups should score differently on the measure(s) or instrument(s) under evaluation, in this case EQ-5D-5L. Known-group comparisons and hypotheses about the expected effects were formulated beforehand and were based on the literature and clinical experience. Patients who had not received a BR after mastectomy, had experienced a complication, had received radiotherapy, or who were of an older age were hypothesized to have a (relatively) lower QoL and therefore a lower score EQ-5D-5L. Patients with an A-BR were hypothesized to have a higher QoL and higher EQ-5D-5L scores/values than I-BR patients.[17,18] EQ-5D-5L outcomes for BR patients were not expected to significantly differ from Dutch general population reference data. To test this hypothesis, we used the raw data from the official Dutch EQ-5D-5L valuation study. This is a large representative study with 1000 respondents (505 females) from the general public, which is now used as the mandatory reference study for EQ-5D-5L in health economic evaluations in the Netherlands.[2,10] A skewed EQ-5D-5L distribution score was expected, as EQ-5D-5L is a generic quality of life questionnaire and most patients were expected to have few side effects by comparison with impact of the BR. Given the expected skewed distribution of outcomes, the group comparisons were performed using the non-parametric Wilcoxon rank-sum (for 2-group comparisons) and Kruskal-Wallis equality-of-populations rank tests (>2-groups).

We performed propensity score matching to control for differences in pretreatment patient characteristics in group comparisons directly related to the treatment modality by using the PSMATCH3 module for SPSS.[19,20] Three consecutive matching procedures were performed. First, the A-BR and I-BR cohorts were matched on pretreatment clinical and socio-demographic characteristics (Table 1). Subsequently, MAS was matched with the combined matched BR cohort on clinical characteristics, because socio-demographic characteristics were not available for all patients in this cohort. Finally, the Dutch general population reference sample was age and sex matched to the combined matched BR and MAS cohorts.

Convergent and Discriminant Validity

Convergent validity is based on the idea that items or scales that measure a similar concept should be strongly correlated to each other, whereas other items or scales that measure concepts that are unrelated should have a weak correlation to one another, which indicates discriminant validity. The convergent and discriminant associations were hypothesized beforehand and were assessed using non-parametric Spearman rank correlation coefficients. The following criteria for correlation strength, as formulated by Cohen, were utilized: weak for $0.1 \leq rs < 0.3$, moderate for $0.3 \leq rs < 0.5$ and strong for $rs \geq 0.5$.[21] For statistical testing, two-sided p-values ≤ 0.05 were considered statistically significant. Statistical analyses were performed using IBM® SPSS Statistics version 24 for Mac OSX.

Results

Socio-demographic and Clinical Characteristics

The original unmatched cohorts consisted of 202 A-BR, 103 I-BR, and 158 MAS patients and showed: a relatively large imbalance in age (with a disproportionate proportion older than 70 years in the MAS cohort), laterality of the mastectomy, reconstruction status, breast cancer recurrence, chemotherapy and hormone therapy. Table 1 shows the socio-demographic and clinical characteristics of both the unmatched and matched cohorts of A-BR and I-BR patients in addition to two reference cohorts that were used, a MAS cohort and an age-sex matched sample of the general population. The matching procedures resulted in a largely balanced cohort, with no statistically significant differences between the A-BR and I-BR cohort on the matched pretreatment patient characteristics.

Table 1. Sociodemographic and clinical characteristics of patient samples

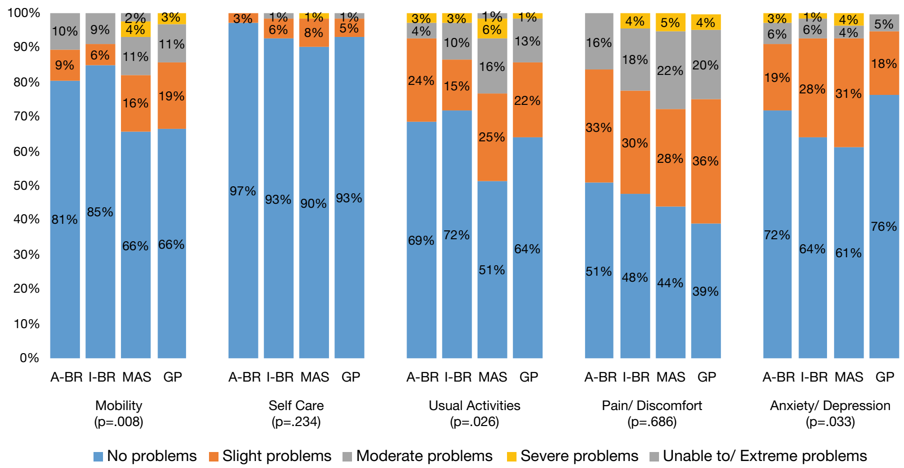
	Unmatched cohort				Matched cohorts			
	A-BR	I-BR	MAS	D-GP	A-BR	I-BR	MAS	D-GP
N	202	103	158	505	67	67	134	268
Age, median (SD)	55^{a} (9.28)	53^{a,c} (12.22)	63^{b} (11.94)	47^{a,b} (17)	55^{a} (9.49)	55^{a} (11.63)	61^{b} (10.97)	58^{a,b} (11)
Year of BC diagnosis, median (SD)	2008^{a} (5.23)	2007^{a} (6.64)	2003^{b} (7.95)	N/A	2007^{a} (6.27)	2006^{a,b} (7.26)	2003^{b} (7.85)	N/A
Year of mastectomy, median (SD)	2008^{a} (4.84)	2007^{a} (6.31)	2006^{b} (6.35)	N/A	2008^{a} (6.19)	2007^{a} (6.87)	2007^{a} (5.74)	N/A
Year of first BR, median (SD)	2011^{a} (4.29)	2009^{a} (7.18)	2010^{a,b} (11.38)	N/A	2010^{a} (5.77)	2009^{a} (6.66)	2014^{a} (2.13)	N/A
Year of last BR, median (SD)	2013^{a} (2.89)	2012^{a} (3.51)	2015^{a} (1.15)	N/A	2013^{a} (2.78)	2012^{a} (4.21)	2015^{a} (1.15)	N/A
Laterality mastectomy								
Unilateral	179^{a} (88.6%)	48^{b} (46.6%)	71^{a} (83.5%)	N/A	46^{a} (68.7%)	47^{a} (70.1%)	64^{a} (85.3%)	N/A
Bilateral	23^{a} (11.4%)	55^{b} (53.4%)	14^{a} (16.5%)	N/A	21^{a} (31.3%)	20^{a} (29.9%)	64^{a} (85.3%)	N/A
Reconstruction status								
Unilateral BR	175^{a} (86.6%)	46^{b} (44.7%)	1^{c} (1.2%)	N/A	44^{a} (65.7%)	45^{a} (67.2%)	0 (0.0%)	N/A
Bilateral BR	26^{a} (12.9%)	56^{b} (54.4%)	0 (0.0%)	N/A	22^{a} (32.8%)	22^{a} (32.8%)	0 (0.0%)	N/A
Previously had a BR	1^{a} (0.5%)	1^{a} (1.0%)	9^{b} (10.6%)	N/A	1^{a} (1.5%)	0 (0.0%)	8^{b} (10.7%)	N/A
Never had BR and doesn't want BR	0 (0.0%)	0 (0.0%)	70^{a} (82.4%)	N/A	0 (0.0%)	0 (0.0%)	61^{a} (81.3%)	N/A
Never had BR but wants BR	0 (0.0%)	0 (0.0%)	5^{a} (5.9%)	N/A	0 (0.0%)	0 (0.0%)	5^{a} (6.7%)	N/A
Patient reported complications								
None	106^{a} (52.5%)	46^{a} (44.7%)	6^{b} (3.8%)	N/A	37^{a} (55.2%)	34^{a} (50.7%)	4^{b} (3.0%)	N/A
Yes	80^{a} (39.6%)	47^{a} (45.6%)	7^{b} (4.5%)	N/A	24^{a} (35.8%)	26^{a} (38.8%)	7^{b} (5.3%)	N/A
N/A	16^{a} (7.9%)	10^{a} (9.7%)	144^{b} (91.7%)	N/A	6^{a} (9.0%)	7^{a} (10.4%)	122^{b} (91.7%)	N/A
Breast Cancer Recurrence								
No recurrence	183^{a} (90.6%)	82^{b} (79.6%)	122^{b} (77.2%)	N/A	57^{a} (85.1%)	55^{a} (82.1%)	101^{a} (75.4%)	N/A
Local recurrence	10^{a} (5.0%)	13^{b} (12.6%)	21^{b} (13.3%)	N/A	7^{a} (10.4%)	8^{a} (11.9%)	19^{a} (14.2%)	N/A
Distant recurrence	9^{a} (4.5%)	8^{a} (7.8%)	15^{a} (9.5%)	N/A	3^{a} (4.5%)	4^{a} (6.0%)	14^{a} (10.4%)	N/A
Chemotherapy								
Yes	139^{a} (68.8%)	52^{b} (50.5%)	98^{a,b} (62.0%)	N/A	40^{a} (59.7%)	33^{a} (49.3%)	82^{a} (61.2%)	N/A
No	63^{a} (31.2%)	51^{b} (49.5%)	60^{a,b} (38.0%)	N/A	27^{a} (40.3%)	34^{a} (50.7%)	52^{a} (38.8%)	N/A
Radiotherapy								
Yes	74^{a} (36.6%)	27^{a} (26.2%)	84^{b} (53.2%)	N/A	16^{a} (23.9%)	19^{a} (28.4%)	64^{b} (47.8%)	N/A
No	128^{a} (63.4%)	76^{a} (73.8%)	74^{b} (46.8%)	N/A	51^{a} (76.1%)	48^{a} (71.6%)	70^{b} (52.2%)	N/A
Hormone therapy								
Currently undergoing treatment	49^{a} (24.3%)	18^{a} (17.5%)	58^{b} (36.7%)	N/A	13^{a} (19.4%)	11^{a} (16.4%)	40^{a} (29.9%)	N/A
Treated	66^{a} (32.7%)	21^{a,b} (20.4%)	22^{b} (13.9%)	N/A	20^{a} (29.9%)	14^{a} (20.9%)	21^{a} (15.7%)	N/A
Not treated	87^{a} (43.1%)	64^{b} (62.1%)	78^{a,b} (49.4%)	N/A	34^{a} (50.7%)	42^{a} (62.7%)	73^{a} (54.5%)	N/A
Employment status								
Yes, outdoor	117^{a} (60.3%)	61^{a} (64.2%)	N/A	N/A	43^{a} (68.3%)	41^{a} (67.2%)	N/A	N/A
Yes, inhome	19^{a} (9.8%)	8^{a} (8.4%)	N/A	N/A	3^{a} (4.8%)	6^{a} (9.8%)	N/A	N/A
No	58^{a} (29.9%)	26^{a} (27.4%)	N/A	N/A	17^{a} (27%)	14^{a} (23.0%)	N/A	N/A
Participation in social activities								
Rarely	16^{a} (8.2%)	8^{a} (8.2%)	N/A	N/A	5^{a} (7.8%)	4^{a} (6.5%)	N/A	N/A
Average	112^{a} (57.1%)	49^{a} (50.0%)	N/A	N/A	35^{a} (54.7%)	28^{a} (45.2%)	N/A	N/A
Often	68^{a} (34.7%)	41^{a} (41.8%)	N/A	N/A	24^{a} (37.5%)	30^{a} (48.4%)	N/A	N/A
Living arrangement								
1 person household	30^{a} (15.5%)	19^{a} (19.2%)	N/A	N/A	14^{a} (22.2%)	14^{a} (22.2%)	N/A	N/A
Multiperson househol	164^{a} (84.5%)	80^{a} (80.8%)	N/A	N/A	49^{a} (77.8%)	49^{a} (77.8%)	N/A	N/A
Children in household								
Yes	103^{a} (52.8%)	50^{a} (51.0%)	N/A	N/A	36^{a} (56.3%)	27^{a} (42.9%)	N/A	N/A
No	92^{a} (47.2%)	48^{a} (49.0%)	N/A	N/A	28^{a} (43.8%)	36^{a} (57.1%)	N/A	N/A
Education								
Elementary school	0 (0.0%)	2^{a} (2.1%)	N/A	N/A	0 (0.0%)	2^{a} (3.2%)	N/A	N/A
Lower-level profesional schooling	31^{a} (16.3%)	10^{a} (10.3%)	N/A	N/A	4^{a} (6.5%)	6^{a} (9.5%)	N/A	N/A
Mid-level highschool	44^{a} (23.2%)	19^{a} (19.6%)	N/A	N/A	15^{a} (24.2%)	13^{a} (20.6%)	N/A	N/A
Mid-level profesional schooling	41^{a} (21.6%)	21^{a} (21.6%)	N/A	N/A	14^{a} (22.6%)	12^{a} (19.0%)	N/A	N/A
Upper-level highschool	23^{a} (12.1%)	16^{a} (16.5%)	N/A	N/A	6^{a} (9.7%)	9^{a} (14.3%)	N/A	N/A
Higher-level professional schooling	35^{a} (18.4%)	22^{a} (22.7%)	N/A	N/A	15^{a} (24.2%)	15^{a} (23.8%)	N/A	N/A
Academic schooling	16^{a} (8.4%)	7^{a} (7.2%)	N/A	N/A	8^{a} (12.9%)	6^{a} (9.5%)	N/A	N/A

Values in the same row and sub-table not sharing the same superscript are significantly different at $p < .05$ in the two-sided test of equality for column proportions. Cells with no superscript are not included in the test. BR (breast reconstruction), A-BR (autologous BR), I-BR (implant BR), MAS (mastectomy not followed by BR), D-GP (Dutch age-sex matched reference population). A-BR, I-BR and MAS cohorts were propensity score matched. D-GP cohort was age-sex matched.

Distribution of EQ-5D-5L Health Profiles

Figure 1 illustrates the distribution of responses to the individual dimensions for all samples. One-to-one comparisons between the matched BR cohorts (i.e. A-BR and I-BR) did not show statistically significant differences on any of the EQ-5D-5L dimensions. Comparisons between the BR and Dutch general population (D-GP) cohorts on the individual dimensions also showed no statistically significant differences. Finally, comparisons between the BR and MAS cohorts showed substantial differences which were statistically significant for the 'mobility' and 'usual activities' dimensions (both p<.001).

Figure 1. EQ-5D-5L responses in matched samples of A-BR (n=67) I-BR (n=67) and MAS patients (n=134) and Dutch general population (n=268)



All comparisons were tested using Kruskal-Wallis equality-of-populations rank test. A-BR (autologous breast reconstruction), I-BR (implant breast reconstruction), MAS (mastectomy not followed by breast reconstruction), D-GP (Dutch age-sex matched reference general population). A-BR, I-BR and MAS cohort were propensity score matched. D-GP cohort was age-sex matched. (Stolk, 2016)

Table 2 depicts the most frequently occurring EQ-5D-5L health profiles in the different cohorts and allows the evaluation of a potential ceiling effect. The unmatched cohorts are presented in this table because comparisons are made within and not between patient groups. In total, 69 unique health profiles were reported in the BR cohorts. Thirty-one percent of A-BR patients and 35% of I-BR patients reported no problems on any of the five dimensions (health profile 11111), making it the most frequent health profile in these cohorts, similar to that of the D-GP. This ceiling effect was less pronounced among MAS patients where 24.7% reported perfect health in the unmatched cohort. To further explore this ceiling effect, an aggregated mean score of the Breast-Q 'psychosocial', 'chest and upper body' and 'abdomen' well-being scores was calculated for each BR patient.

We found that over three quarters of BR patients with an EQ-5D-5L score of 1.00 had an aggregated Breast-Q score of 80 or higher compared to only 22 percent of BR patients that had an EQ-5D-5L score lower than 1.00. This suggests that the ceiling effect on EQ-5D-5L represented patients that indeed experienced very few or no problems with regard to their BR-related well-being and consequently did not necessarily represent insensitivity of EQ-5D-5L to BR-related QoL problems.

Table 2. Most frequently occurring EQ-5D-5L Health Profiles in unmatched BR cohorts

Health profile	A-BR	I-BR	MAS	D-GP
11111	63 (31.2%)	36 (35%)	39 (24.7%)	179 (35.4%)
11121	25 (12.4%)	9 (8.7%)	10 (6.3%)	63 (12.5%)
11112	12 (5.9%)	8 (7.8%)	9 (5.7%)	19 (3.8%)
11221	12 (5.9%)	5 (4.4%)	6 (3.8%)	21 (4.2%)
11122	11 (5.4%)	8 (7.8%)	5 (3.2%)	15 (3%)
11131	7 (3.5%)	3 (2.9%)	3 (1.9%)	7 (1.4%)
11222	3 (1.5%)	3 (2.9%)	4 (2.5%)	5 (1%)
21121	3 (1.5%)	2 (1.9%)	2 (1.3%)	5 (1.6%)

Health profile denoting the respective level of the following dimensions in the order: Mobility, Self-Care, Usual Activities, Pain/ Discomfort, Anxiety/ Depression. 1 "no problems" up to 5 "severe problems/unable to". All health profiles that occurred five or more times in the unmatched BR cohort are listed. BR (breast reconstruction), A-BR (autologous BR), I-BR (implant BR), MAS (mastectomy not followed by BR), D-GP (Dutch age-sex matched reference population).

Known-group Validity

The findings above were based on the dimensions and profiles of the EQ-5D-5L, attributes common to QoL questionnaires. A key feature of EQ-5D-5L is the utility score, which can be used in economic evaluations. The results based on this utility score are presented in an overview of the known-group comparisons in Table 3. Contrary to our hypothesis, no statistically significant differences between the A-BR and I-BR patient groups were found using EQ-5D-5L utility scores. As hypothesized, BR yielded a statistically significant better QoL compared to MAS. Breast cancer patients who had undergone a BR did not show a statistically significant different QoL compared to the D-GP. Patients who had experienced a complication following BR reported a statistically significant lower mean QoL than patients who had not experienced a complication.

Table 3. Known-group comparisons

	EQ-5D-5L			
Age *	Count	Mean	Standard Deviation	p-value
<50	387	.867	.17	.87
50-60	244	.839	.18	
60-70	222	.831	.18	
>70	115	.786	.20	
Cohorts				
BR	305	.844	.18	
BR (matched)	134	.863	.16	
A-BR	202	.840	.18	
A-BR (matched)	67	.872	.14	
I-BR	103	.851	.17	
I-BR (matched)	67	.853	.18	
MAS	158	.792	.20	
MAS (matched)	134	.798	.20	
D-GP	268	.841	.16	
A-BR v I-BR				.89 (matched .70)
BR v MAS				.00 (matched .00)
BR v GP				.49 (matched .15)
MAS v GP				.01 (matched .03)
All groups				.00 (matched .00)
Patient reported complications *				.00
None	152	.872	.16	
Yes	127	.806	.19	
Reconstruction status *				.56
Unilateral BR	222	.836	.19	
Bilateral BR	82	.859	.15	
Radiotherapy *				.06
Yes	101	.857	.19	
No	204	.837	.17	

All comparisons were tested using Kruskal-Wallis equality-of-populations rank test. Matched (propensity score matched), BR (breast reconstruction), A-BR (autologous BR), I-BR (implant BR), MAS (mastectomy not followed by BR), D-GP (Dutch age-sex matched reference population). The group comparisons marked with * were performed on the unmatched BR cohort. The outcome values in this table are based on a sample from an academic hospital, may not be representative for the BR population as a whole, and are solely illustrative of the ability of EQ-5D-5L to detect differences between relevant groups. Hence, these outcomes should not be used as EQ-5D-5L reference values in scientific studies.

Convergent and Discriminant Validity

Table 4 shows the correlations of moderate strength or higher between the QoL of EQ-5D-5L and its individual dimensions on the one hand, and the Breast-Q scales and EORTC scales for the unmatched BR cohorts on the other. Predefined hypotheses about convergence and divergence of correlations were used to assess validity and are depicted in Table 4.

Table 4. Convergent and discriminant validity between EQ-5D-5L dimensions, EQ-5D-5L and other quality of life measures.

EuroQol-5D-5L Dimensions and scores:	Mobility	Self Care	Usual Activities	Pain/ Discomfort	Anxiety/ Depression	EQ-5D-5L NL
Breast-Q condition-specific QoL-measure						
Psychosocial Well-being	-.288**	-.250**	-.335**	-.390**	-.501**	.524**
Sexual Well-being	-.223**	-.249**	-.249**	-.240**	-.417**	.401**
Physical Well-being:						
Chest and Upper Body	-.204**	-.249**	-.409**	-.561**	-.266**	.516**
Physical Well-being:						
Abdomen	-.322**	-.191**	-.427**	-.474**	-.228**	.484**
EORTC QLQ-C30 cancer-specific QoL-measure						
Global health status/QoL	-.332**	-.291**	-.443**	-.464**	-.414**	.553**
Physical Function	-.555**	-.274**	-.613**	-.505**	-.269**	.599**
Role Function	-.428**	-.266**	-.690**	-.606**	-.276**	.634**
Emotional Function	-.188**	-.237**	-.378**	-.382**	-.614**	.547**
Cognitive Function	-.213**	-.250**	-.352**	-.353**	-.339**	.414**
Social Function	-.290**	-.246**	-.465**	-.383**	-.389**	.497**
Fatigue	.329**	.250**	.530**	.522**	.384**	-.595**
Pain	.460**	.294**	.627**	.744**	.279**	-.704**
Insomnia	.290**	.133*	.398**	.412**	.308**	-.465**
Appetite loss	.168**	.220**	.336**	.301**	.317**	-.375**
EORTC QLQ-B23 breast cancer-specific QoL-measure						
Body image	-.222**	-.218**	-.313**	-.299**	-.395**	.430**
Future perspective	-.199**	-.239**	-.295**	-.288**	-.485**	.442**
Systemic therapy	.262**	.248**	.400**	.384**	.287**	-.458**
Breast symptoms	.231**	.235**	.355**	.478**	.188**	-.435**
Arm symptoms	.235**	.284**	.490**	.499**	.190**	-.485**

Only scales with at least one correlation of moderate strength (0.35-0.50) or higher are shown. Correlations that were hypothesized to show a convergent correlation are highlighted in dark grey with a fine border. Correlations that were hypothesized to show a discriminant correlation are highlighted in light grey with a thick border. Correlations of moderate strength (0.35-0.50) are printed in italics, strong correlations (>0.50) are in bold. ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed).

Most scales relevant to BR surgery showed at least moderate correlation with EQ-5D-5L. A notable exception to this finding were the dimensions of the Breast-Q that measured patient satisfaction with either the breast or outcome, because they showed weak correlations with EQ-5D-5L (r=0.345 and r=0.327, respectively).

Discussion

This is the first study to evaluate the validity of EQ-5D-5L in patients who received a BR after having undergone a mastectomy for the treatment of breast cancer. Evaluation of the validity of this outcome measure is important as EQ-5D-5L is currently the preferred QoL outcome measure in cost-effectiveness evaluations that inform healthcare policymakers and reimbursement agencies. EQ-5D-5L was able to discriminate between several, but not all, patient groups and outcomes. Good convergent and discriminant validity of both EQ-5D-5L and its individual dimensions was demonstrated. Furthermore, additional support for validity was revealed by moderate correlations between the generic EQ-5D-5L and specific QoL aspects of BR like such as sexuality and body image.

Distribution and ceiling effect of EQ-5D-5L health profiles

One aspect on which the discriminative ability of a measure is frequently judged, is its ability to detect differences between a given sample/cohort and the general population.[16] However, there was a large resemblance in the distribution of EQ-5D-5L responses to the EQ-5D-5L of patients who had received a BR and that of the age-sex matched cohort of the Dutch general population, with no statistically significant differences. Normally speaking, these findings would limit the validity of the outcome measure. However, in the case of BR this may not necessarily be the case. Given that the overall aim of BR is to restore the QoL of breast cancer patients to a level comparable with that before they were afflicted by breast cancer, and that women eligible for a BR may represent a relatively healthy patient group, outcomes comparable to the general population could be expected and were, indeed, hypothesized in this study. Further analysis of the distribution of responses (Figure 1 and Table 3) showed that EQ-5D-5L can detect statistically significant differences between BR and MAS patients on both the 'mobility' and 'usual activities' EQ-5D-5L dimensions, indicating sensitivity of the instrument. In our BR-cohort a considerable ceiling effect was found which can be considered a psychometric problem in terms of sensitivity.[16] EQ-5D dimensions might not tap into the relevant dimensions of QoL following BR, benefits of BR might go undetected, and the (cost-) effectiveness of BR would thus be underestimated. However, a ceiling effect may only represent a problem if it meant that the instrument is insensitive to problems actually present in the sample at hand. We found that the EQ-5D-5L ceiling effect represented patients that did indeed experience very few or no problems with respect to their BR-related well-being. Hence, we believe that the ceiling effect does not present a major problem in calculating a valid cost-effectiveness ratio in economic evaluations of BR.

Known-group Validity

A-BR vs I-BR

Currently, the only utilities available that differentiate between different BR techniques were obtained through expert opinion interviews with plastic surgeons, generally considered an inappropriate method for eliciting such values.[5-7] In these studies surgeons estimated that A-BR resulted in the highest utility (0.83) followed by I-BR (0.66) and mastectomy not followed by BR (0.63).[17,18] However, in the known-group comparison no significant differences were found on the EQ-5D-5L between A-BR or I-BR in either the matched or unmatched cohorts. Since previous utility studies used controversial methods, it is difficult to determine whether EQ-5D-5L was unable to detect differences between A-BR and I-BR because there were no substantial differences in QoL or because of lack of sensitivity of the measure. As EQ-5D-5L also showed convergent associations with the reference measures on 4 out of 5 dimensions, we consider the former more likely.

BR vs MAS

EQ-5D-5L was able to discriminate between BR and MAS patients both in an uncorrected and a matched cohort. Patients who had received a BR after their mastectomy had significantly better EQ-5D-5L scores than patients who had not received a BR. This result corresponds with the findings of previous studies which also reported better QoL of BR patients compared to MAS patients, but conflicts with other studies that show little to no difference.[22-27] It appears that more recent studies have been more successful in finding significant differences between both patient groups, especially when making use of the Breast-Q questionnaire. This may be due to improved surgical techniques, improved sensitivity of QoL instruments, or a significant difference between groups may after all not exist. A systematic review or a meta-analysis comparing the QoL of MAS vs BR could help inform us of the true effect on QoL of BR.

Complications vs no complications after BR

As hypothesized, patients who had experienced complications following their BR had a poorer mean QoL assessed with EQ-5D-5L.

Convergent and Discriminant Validity

The EQ-5D-5L dimensions 'mobility', 'usual activities', 'pain/discomfort', and 'anxiety/depression' showed strong correlations with the domains and scales of similar concepts on both the BR-specific Breast-Q and EORTC cancer and breast cancer specific measures, which implies good *convergent validity* of EQ-5D-5L for BR. These correlations were considerably higher than those with dissimilar dimensions, which indicates good *discriminant validity* of EQ-5D-5L for BR. The EQ-5D-5L dimension 'self-care' showed only weak correlations with the other measures, which is probably explained by a lack of variance: the vast majority of BR patients (94.3%) reported no problems on this dimension. This result was also seen in the age- and sex-matched Dutch general population (Figure 1).

There are two important aspects of QoL in relation to BR, assessed by the Breast-Q and EORTC-BR23, that are worth highlighting since EQ-5D-5L is potentially insensitive to these features, namely 'sexuality' and 'body image'.[28,29] Both had correlations of moderate strength with the 'anxiety/depression' scale.

Conclusions

EQ-5D-5L was able to discriminate between various relevant patient groups and outcomes. It was not able, however, to discriminate between A-BR vs I-BR and BR vs general population. Convergent and discriminant validity of both the individual EQ-5D-5L dimensions and of EQ-5D-5L was demonstrated by strong correlations with measures employing similar concepts. Furthermore, EQ-5D-5L showed correlations of moderate strength with QoL aspects important to BR patients: sexuality and body image. In conclusion, EQ-5D-5L showed sufficient validity to be used as one of the primary outcome measures in the evaluation of QoL outcomes in patients who have undergone a postmastectomy BR for breast cancer treatment. The next step will be to obtain representative EQ-5D-5L reference values for this patient population.

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Chapter 3

Long-term health-related quality of life after four common surgical treatment options for breast cancer and the effect of complications – a retrospective patient-reported survey among 1871 patients

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Plastic Reconstructive Surgery, 2020, 146(1):1-13.

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Abstract

Background
Differences in health-related quality of life (HRQoL)-outcomes after different surgical breast cancer treatment options, including breast reconstruction (BR), are relevant for counseling individual patients in clinical decision-making, and for (societal) evaluations such as (cost-) effectiveness analyses. However, current literature shows contradictory results, due to use of different Patient-Reported Outcome Measures (PROMs) and study designs with limited patient numbers. Therefore, this article sets out to improve this evidence from a clinical and societal perspective using PROMs in a large, cross-sectional study for different surgical breast cancer treatment options.

Methods
HRQoL was assessed through the EQ-5D-5L, EORTC-QLQ-C30/-BR23 and Breast-Q. Patients with different treatments (breast conserving surgery (BCS), mastectomy (MAS), autologous BR (A-BR), implant-based BR (I-BR)) were compared after propensity-weighted adjustment of pre-treatment differences. The EQ-5D was used to value the effect of surgical complications.

Results
1871 breast cancer patients participated (BCS: n=615, MAS: n=507, A-BR: n=330, I-BR: n=419). MAS-patients reported the lowest mean HRQoL based on the EQ-5D (MAS:0.805, BCS:0.844, A-BR:0.849, I-BR:0.850) and functioning scores of the EORTC-QLQ-C30. Based on the Breast-Q, A-BR-patients had higher mean satisfaction with outcome and satisfaction with breasts and had higher sexual well-being scores than I-BR patients. Patients with complications (except for I-BR) reported statistically significant lower HRQoL than patients without complications. Complications in A-BR patients resulted in a substantially lower HRQoL than in I-BR patients.

Conclusions
Our study shows the added value of breast conservation and reconstruction compared to mastectomy, however, differences between BCS, I-BR, and A-BR were subtle. Complications resulted in poorer HRQoL.

Introduction

Because five-year survival rates for early stage breast cancer are relatively high,[1,2] the effects of breast cancer and its treatment on quality of life become more important, which may affect surgical decision-making. Since mastectomy (MAS) and breast conserving surgery (BCS) including radiotherapy have similar disease-free and overall survival,[3-5] the effects of different treatment modalities on outcomes other than survival gain significance. Because loss of a breast may negatively affect psychosocial health, body image, and sexual function,[6] guidelines recommend that the possibility of breast reconstruction (BR) should be discussed with every patient scheduled for MAS.[7-9] Multiple options are available, either using autologous tissue (autologous BR, A-BR) or breast implants (implant BR, I-BR), varying in costs, timing, duration, complication rates, and cosmetic results.[6,10,11] BR aims to improve the patient's well-being and health-related quality of life (HRQoL),[6,10] but patients opting for BR also have a risk of complications,[12-15] reconstruction failure,[12,13] or disappointing (cosmetic) results.[6] Consequently, shared decision-making (SDM) between physicians and patients about the preferred surgical treatment is a complex trade-off between outcomes and risks.

HRQoL-outcomes after different surgical breast cancer treatment options are relevant for counseling individual patients in clinical decision-making, and for societal evaluations as cost-effectiveness analyses used in health policy. Research shows that post-treatment HRQoL is relatively high in breast cancer patients, but evidence about (differences in) HRQoL after different treatment options is conflicting.[16-19] This conflicting evidence may be explained by variation in the use of patient-reported outcome measures (PROMs), study designs, and patient populations. For instance, there are both studies that have and have not found differences in HRQoL between patients who had undergone BCS or MAS.[20] Also, several higher quality studies did not find statistically significant differences in HRQoL, body image, and sexuality between patients with or without BR.[21] We believe that evidence should be improved, as such information is relevant for choosing a treatment in clinical decision-making and for health policy. Until now, outcomes have been generally measured in small, cross-sectional, mono-center studies. Ideally, one would include all surgical options relevant to breast cancer patients in one large prospective cohort study.[21] Santosa et al. performed such a large prospective study, comparing patients with I-BR and A-BR.[22] Furthermore, outcomes measured over a longer period of time would be of interest, as different surgical outcomes may have a different HRQoL-course over time. For example, recovery from surgical complications will take additional time.

To improve the evidence on the impact of breast cancer surgery and consequently for clinical decision-making and health policy, the present study aimed to compare HRQoL outcomes for four common surgical breast cancer treatment options (BSC, MAS, A-BR, I-BR). HRQoL was assessed using multiple PROMs in a large, multicenter, retrospective, cross-sectional cohort of breast cancer patients up to ten years after diagnosis. The second aim was to investigate the impact of complications on HRQoL following these different surgical treatment options. We hypothesized that BCS and A-BR are favorable over I-BR and MAS in terms of HRQoL, however, in the absence of complications, with MAS yielding the least preferable outcomes.

Methods

Study population

Female breast cancer patients (n=3,804) from four hospitals in the Netherlands (one academic hospital, three general hospitals) were invited by mail to participate in a self-administered cross-sectional online survey. Patients were included if they had been surgically treated for non-metastatic breast cancer in the last ten years (2008-2018). Patients who had developed distant metastases since curative treatment or who were not proficient in Dutch were excluded. Four groups were formed based on the surgical procedure: BCS, MAS, A-BR, or I-BR. Time between surgery and invitation was over 6 months, to ensure patients had recovered from the treatment. Patients who preferred completing a paper questionnaire, were sent one on request. Respondents gave informed consent for processing their coded survey results. The Medical Ethics Committee of the Erasmus MC reviewed and approved the study protocol (MEC-2015-273).

Measures

The survey included questions regarding baseline patient and treatment characteristics, including surgical complications, and the following validated questionnaires:

EQ-5D-5L. This questionnaire of health status measures problems in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), all with five levels of severity (no, slight, moderate, severe, and extreme problems). Per health state, a 'value' can be assigned, where 0.00 and 1.00 represent the value for death and perfect health, respectively. This 'value' is also referred to as utility, index score, or preference. The EQ-5D includes values of the general public in the valuation of HRQoL, resulting in 'preference-weighted QoL scores', often referred to as 'utilities'. Utilities are used as outcomes in economic evaluations, which can inform health policy. A mean general population (GP) reference was obtained to compare study results to that of a sample of the Dutch general population.[23]

EORTC QLQ-C30/BR23. The EORTC Quality of Life Questionnaires (QLQ) measures HRQoL in cancer patients,[24] the breast cancer-specific QLQ-BR23 supplements the cancer-specific QLQ-C30.[25] Both consist of functioning and symptom scales; the QLQ-C30 also includes a global health status scale. All items and scales range from 0 to 100, with higher scores presenting a higher level of functioning or general health for the functional and global health status scales, respectively, and higher scores representing a higher level of symptoms for the symptom scales.[26]

Breast-Q. A treatment-specific PROM, developed to measure breast-related QoL and satisfaction, on several HRQoL domains. Six postoperative domains were used from the different modules which were developed for the respective patient groups: 'Satisfaction with Breasts', 'Satisfaction with Outcome', 'Psychosocial Well-being', 'Sexual Well-being', 'Physical Well-being Chest', 'Physical Well-being Abdomen'. The raw scores of the Breast-Q domains were converted to scores between 0 (worst) and 100 (best) using the Q-score software.[27]

Analyses

Twenty-five patients did not report their highest completed education level; these missing answers were imputed using a single imputation method. A propensity-score weighting for multiple treatments was calculated according to the method of McCaffrey et al.[28] to adjust for covariates that predict receiving either one of the four surgical treatment options, thereby reducing the effects of confounding. The following clinical and sociodemographic characteristics were included in the propensity weight calculation: age at time of survey, education, year of breast cancer diagnosis, year of surgery, chemotherapy, hormone therapy, and breast cancer recurrence. The EQ-5D Dutch general population reference sample (GP) was matched to all surgical groups using age and sex as the matching variables. Propensity weights were calculated by the Toolkit for Weighting and Analysis of Non-equivalent Groups (TWANG) Package for STATA.[29]

For all responding patients, propensity-adjusted patient and treatment characteristics and HRQoL were presented. Propensity weights were incorporated in the analyses using the Stata-SE14 survey (svy) post-estimation function.[30] Mean scores, confidence intervals, and pair-wise comparisons were subsequently obtained and performed using the margins regression estimation function. Column proportions were chi-squared tested. The utilities resulting from the EQ-5D per surgical treatment were stratified by experienced surgical complications. Utilities per surgical treatment were plotted over the course of time in three-year intervals (≤3; 3≤6; 6≤9; >9), starting at time of last BR.
For statistical testing, two-sided p-values ≤0.05 were considered statistically significant. All analyses were performed in StataCorp Stata-SE14.[31]

Results

1,871 out of 3,804 patients (49%) responded, consisting of 615 BCS, 507 MAS, 330 A-BR, and 419 I-BR patients. Table 1 presents patient and treatment characteristics. Nearly all A-BR procedures were abdominally-based free-flap reconstructions. After propensity-weighted adjustment, estimated group sizes were reduced to 434.0 BCS, 386.3 MAS, 178.6 A-BR, and 295.5 I-BR patients. Group sizes declined as patients with certain characteristics from one group occurred less frequently in another group, and thus received a relative score weight lower than 1. After propensity-weighted adjustment, balance was achieved for all variables, except for age and chemotherapy treatment.

Table 1. Patient-Reported Characteristics of 1871 Breast Cancer Patients per Surgical Treatment Group, before and after Propensity-Weighted Adjustment

	Groups before propensity-weighted adjustment				Groups after propensity-weighted adjustment			
	BCS	**MAS**	**A-BR**	**I-BR**	**BCS**	**MAS**	**A-BR**	**I-BR**
Group size (n)	**615**	**507**	**330**	**419**	**434**	**386.3**	**178.6**	**295.5**
Time variables, mean (SD)								
Age (in years) at time of survey [X]*	64.43 (9.07)^{a,b}	65.90 (10.67)^{a}	56.35 (9.17)^{b}	55.79 (10.44)^{b}	62.95 (9.67)^{a}	62.23 (10.37)^{a}	59.58 (9.72)^{b}	60.05 (9.96)^{b}
Time (in years) between MAS/BCS - survey [X]	6.14 (3.90)^{a}	7.28 (4.97)^{b}	7.87 (5.18)^{b}	7.65 (5.75)^{b}	7.04 (4.56)^{a}	6.86 (4.34)^{a}	6.61 (4.65)^{a}	7.04 (4.95)^{a}
Time (in years) between BR - survey	N/A	N/A	5.67 (4.76)^{a}	6.20 (5.20)^{a}	N/A	N/A	4.93 (4.34)^{a}	5.75 (4.54)^{b}
Time (in years) between last BR surgery - survey	N/A	N/A	4.54 (4.34)^{a}	4.53 (3.67)^{a}	N/A	N/A	4.01 (3.78)^{a}	4.48 (3.32)^{a}
Treatment characteristics								
Reconstruction status[1]								
Unilateral BR	N/A	N/A	85.6%	64.2%	N/A	N/A	85.4%	71.1%
Bilateral BR	N/A	N/A	14.4%	35.8%	N/A	N/A	14.6%	28.9%
Previously had a BR	N/A	7.8%	N/A	N/A	N/A	8.7%	N/A	N/A
Never had BR and does not want BR	N/A	87.4%	N/A	N/A	N/A	84.9%	N/A	N/A
Never had BR but wants BR	N/A	4.6%	N/A	N/A	N/A	6.4%	N/A	N/A
Timing of reconstruction[1]								
Immediate BR	N/A	N/A	15.9%	46.1%	N/A	N/A	15.6%	47.6%
Delayed BR	N/A	N/A	83.0%	53.5%	N/A	N/A	82.6%	52.0%
Laterality of MAS								
Unilateral	N/A	85.6%	87.9%	67.1%	N/A	86.1%	89.9%	74.4%
Bilateral	N/A	14.4%	12.1%	32.9%	N/A	13.9%	10.2%	25.6%
Recurrence [X]								
No recurrence	93.8%	85.8%	90.9%	89.3%	90.1%	91.0%	91.4%	90.9%
Local recurrence	1.1%	7.7%	5.5%	5.7%	3.5%	4.1%	4.0%	4.5%
Distant recurrence	5.0%	6.5%	3.6%	5.0%	6.4%	4.9%	4.6%	4.5%
Patient-reported complications								
No complication	84.2%	63.5%	56.7%	66.5%	82.3%	64.6%	53.4%	68.4%
Complication	15.8%	22.4%	43.3%	33.5%	17.7%	21.5%	46.6%	31.6%
Unknown	0.0%	14.1%	0.0%	0.0%	0.0%	13.9%	N/A	N/A
Number of comorbidities								
No comorbidities	47.3%	42.2%	51.8%	52.7%	47.1%	48.2%	49.8%	48.7%
1 comorbidity	32.5%	35.3%	30.9%	34.8%	32.6%	34.3%	12.6%	36.4%
2 comorbidities	14.5%	16.6%	12.4%	8.1%	15.0%	13.2%	32.9%	9.4%
3 or more comorbidities	5.7%	5.9%	4.8%	3.9%	4.5%	4.3%	4.7%	4.3%
Treated with:								
Chemotherapy [X]	24.2%	44.2%	63.9%	48.4%	37.4%	42.7%	47.6%	43.9%
Radiotherapy	94.3%	36.9%	35.8%	24.1%	94.9%	33.0%	30.6%	22.6%
Hormone therapy [X]								
Yes, still receiving treatment	19.0%	24.7%	29.1%	24.1%	58.2%	56.3%	57.2%	58.8%
Yes, completed	67.5%	50.3%	48.5%	56.8%	23.8%	23.4%	22.2%	21.6%
Patient characteristics								
Highest completed education [X]								
Lower level	24.9%	28.8%	18.2%	14.6%	24.0%	23.4%	21.5%	18.1%
Mid-level	55.1%	48.1%	56.1%	55.8%	54.5%	53.6%	52.7%	55.3%
High-level professional schooling	20.0%	23.1%	25.8%	29.6%	21.5%	23.1%	25.8%	26.6%
Employment status								
Employed outside home	30.7%	23.5%	54.8%	58.0%	35.3%	31.6%	45.6%	45.6%
Employed from home	1.8%	5.7%	7.9%	4.1%	1.6%	5.1%	10.2%	3.6%
Not employed	52.8%	59.6%	33.0%	32.2%	49.0%	52.4%	37.1%	42.8%
Other	14.6%	11.2%	4.2%	5.7%	14.1%	10.9%	7.2%	8.0%
Household composition								
One person household	19.3%	22.7%	17.6%	15.0%	17.9%	18.8%	22.7%	19.9%
Multi person household	80.7%	77.3%	82.4%	85.0%	82.1%	81.2%	77.4%	80.1%
Relationship status								
Single	7.6%	7.7%	10.9%	9.1%	7.8%	9.2%	9.6%	8.7%
Married	77.9%	74.2%	77.3%	78.3%	79.0%	76.6%	73.5%	76.6%
Divorced	3.6%	4.1%	5.2%	7.4%	3.0%	4.9%	5.9%	8.9%
Widow	10.9%	14.0%	6.7%	5.3%	10.2%	9.3%	10.9%	7.6%
Children								
Yes	19.8%	22.1%	49.1%	48.7%	14.6%	28.1%	42.8%	37.0%
No	80.2%	77.9%	50.9%	51.3%	75.4%	71.9%	57.2%	63.0%

BCS: breast conserving surgery,
MAS: mastectomy without breast reconstruction,
BR: breast reconstruction,
A-BR: mastectomy with autologous BR,
I-BR: mastectomy with implant BR,
GP: general population (Netherlands reference cohort),
SD: standard deviation

Values in the same row and sub-table not sharing the same superscript (^{a,b}) were significantly different at $p<0.05$ using the adjusted Wald test. Cells with no superscript were not included in the test. Tests assume equal variances. SD values for propensity weighted groups are an estimate of the population standard deviation.

[X] Variables used for propensity weighting.

* Mean ages GP-cohort: 46.87 and 58.48 unadjusted and adjusted by propensity score, respectively.

[1] Does not add up to 100% due to missing answers.

Quality of life outcomes

Table 2 presents preference-based HRQoL outcomes at time of survey per group. Unadjusted results for the outcomes presented in this table can be found in the appendix table 1. After propensity-weighted adjustment, patients treated with MAS reported a statistically significant lower mean EQ-5D score (0.805) compared to all other surgical groups (BCS: 0.844; A-BR: 0.849; I-BR: 0.850). Pairwise comparisons of the groups for the individual EQ-5D domains reflected these lower means for MAS as well (Figure 1).

Table 2. Mean patient-reported quality of life scores of 1871 breast cancer patients per surgical treatment and the Dutch general population, after propensity-weighted adjustment

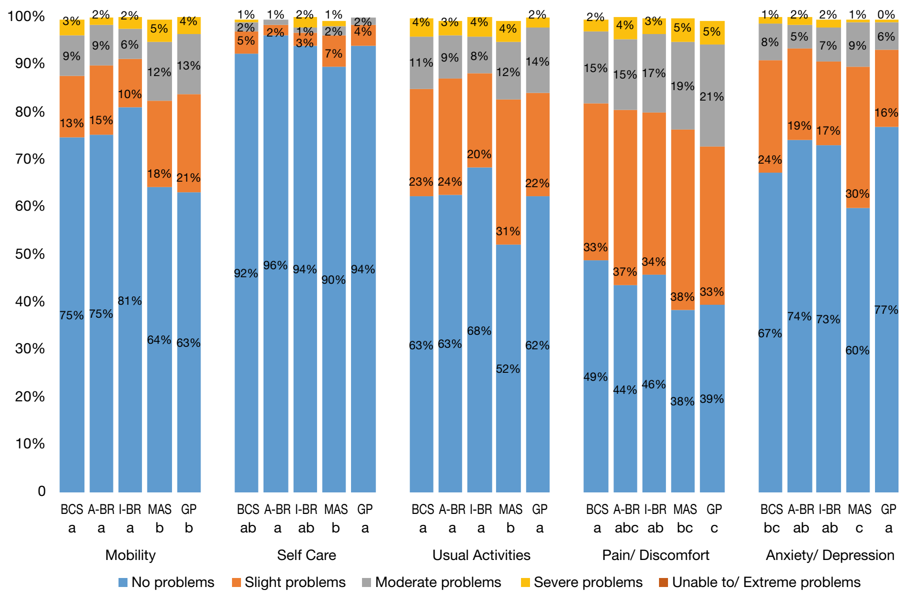
	BCS (95% CI)	MAS (95% CI)	A-BR (95% CI)	I-BR (95% CI)	GP (95% CI)
Group size (n)	**434**	**386.3**	**178.6**	**295.5**	**N/A**
EQ-5D-5L					
Utilities	0.844^{a} (0.829-0.859)	0.805^{b} (0.787-0.823)	0.849^{a} (0.828-0.871)	0.850^{a} (0.823-0.877)	0.833^{a} (0.812-0.854)
VAS Score	77.76^{a} (76.02-79.51)	76.48^{a} (74.75-78.22)	79.24^{a} (76.76-81.72)	77.58^{a} (75.52-79-65)	78.88^{a} (77.08-80.69)
ReEORTC-QLQ-C30					
Global Health Status	80.00^{a} (78.26-81.75)	79.01^{a} (77.14-80.87)	81.38^{a} (79.22-83.54)	80.16^{a} (78.07-82.25)	N/A
Function scales:					
Physical function	84.53^{a} (83.02-86.04)	82.94^{a} (81.32-84.55)	85.62^{a,b} (83.30-87.85)	87.97^{b} (85.63-90.31)	N/A
Role function	84.35^{a} (82.34-86.36)	80.70^{b} (80.84-87.19)	84.02^{a,b} (82.82-89.22)	86.02^{a} (82.82-89.22)	N/A
Emotional function	85.36^{a} (83.36-87.18)	83.84^{a} (81.90-85.78)	87.00^{a} (84.47-89.51)	85.04^{a} (82.40-87.67)	N/A
Cognitive function	84.14^{a} (82.21-86.06)	84.32^{a} (82.32-86.31)	83.67^{a} (80.53-86.82)	84.97^{a} (82.29-87.65)	N/A
Social function	88.82^{a} (87.01-90.63)	86.94^{a} (87.01-90.63)	88.02^{a} (85.54-90.50)	87.48^{a} (84.40-90.55)	N/A
Symptom scales:					
Fatigue	21.82^{a} (19.77-23.87)	22.54^{a} (20.30-24.77)	22.39^{a} (19.27-25.51)	20.21^{a} (17.47-22.94)	N/A
Nausea and vomiting	2.72^{a} (1.98-3.46)	3.31^{a} (2.25-4.38)	2.83^{a} (1.76-3.90)	3.35^{a} (1.40-5.30)	N/A
Pain	15.41a (13.56-17.25)	18.93^{b} (16.53-21.32)	17.18^{a,b} (14.07-20.28)	15.89^{a,b} 12.87-18.90)	N/A
Dyspnea	14.28^{a} (12.18-16.39)	12.22^{a} (10.12-14.31)	13.39^{a} (9.75-17.03)	10.82^{a} (8.06-13.59)	N/A
Insomnia	22.76^{a} (20.09-25.44)	22.69^{a} (19.93-25.44)	20.37^{a} (16.87-23.87)	25.11^{a} (21.10-29.11)	N/A
Appetite loss	5.87^{a} (4.45-7.30)	4.08^{a} (2.90-5.26)	3.81^{a} (2.25-5.37)	3.90^{a} (1.78-6.03)	N/A
Constipation	6.98^{a} (5.38-8.59)	7.07^{a} (5.34-8.79)	7.96^{a} (5.29-10.63)	5.29^{a} (3.80-6.78)	N/A

Table 2. Continued

	BCS (95% CI)	MAS (95% CI)	A-BR (95% CI)	I-BR (95% CI)	GP (95% CI)
Group size (n)	**434**	**386,3**	**178,6**	**295,5**	**N/A**
Diarrhea	4.81^{a} (3.52-6.10)	4.43^{a} (3.14-5.72)	3.24^{a} (1.96-4.51)	4.65^{a} (3.11-6.19)	N/A
Financial problems	5.23^{a} (3.77-6.69)	8.22^{b} (6.16-10.28)	12.30^{b} (8.41-16.19)	7.71^{a,b} (5.21-10.22)	N/A
EORTC-QLQ-BR23					
Function scales:					
Body image	87.45^{a} (85.45-89.45)	80.49^{b} (78.24-82.74)	82.28^{b} (79.01-85.55)	82.35^{b} (79.83-84.88)	N/A
Sexual functioning	27.90^{a} (25.23-30.58)	27.51^{a} (24.80-30.22)	31.95^{a,b} (28.02-35-89)	33.35^{b} (29.99-36.72)	N/A
Sexual enjoyment	57.03^{a} (53.03-61.02)	54.82^{a} (51.07-58.57)	64.24^{b} (59.27-69.21)	63.80^{b} (60.06-67.54)	N/A
Future perspective	74.51^{a} (72.17-76.85)	71.93^{a} (69.15-74.71)	76.14^{a} (72.34-79.95)	75.03^{a} (72.21-77.85)	N/A
Symptom scales:					
Systemic therapy side-effects	12.60^{a} (11.57-13.64)	12.74^{a} (11.49-13.99)	14.41^{a} (12.41-16.40)	13.79^{a} (12.08-15.50)	N/A
Breast symptoms	13.45^{a} (11.80-15.11)	9.94^{b} (8.60-11.28)	8.79^{b} (6.88-10.71)	10.82^{a,b} (8.36-13.27)	N/A
Arm symptoms	12.68^{a} (11.02-14.34)	17.12^{b} (15.12-19.12)	18.18^{b} (14.94-21.41)	16.82^{b} (13.60-20.03)	N/A
Hair loss	4.25^{a} (2.78-5.71)	4.86^{a} (3.37-6.35)	6.50^{a} (4.02-8.98)	5.47^{a} (3.58-7.37)	N/A
BREAST-Q					
Satisfaction with Breasts	65.52^{a} (63.43-67.61)	60.65^{b} (58.79-62.51)	71.29^{c} (68.66-73.92)	59.39^{b} (57.18-61.60)	N/A
Satisfaction with Outcome	N/A	N/A	75.75^{a} (72.52-78.99)	66.37^{b} (63.66-69.08)	N/A
Psychosocial Well-being	73.77^{a} (71.70-75.83)	66.50^{b} (64.68-68.32)	75.78^{a,c} (72.94-78.63)	71.60^{a} (69.30-73.90)	N/A
Sexual Well-being	62.70^{a} (59.92-65.48)	50.00^{b} (47.44-52.55)	63.33^{a} (58.91-67.75)	56.38^{c} (52.88-59.88)	N/A
Physical Well-being: Chest	67.39^{a} (65.17-69.61)	73.47^{b} (71.78-75.16)	75.81^{b,c} (73.56-78.06)	72.64^{b} (70.61-74.66)	N/A
Physical Well-being: Abdomen	N/A	N/A	75.81 (73.56-78.06)	N/A	N/A
Satisfaction Nipple	N/A	N/A	63.03^{a} (58.82-67.25)	54.96^{b} (49.38-60.54)	N/A

BCS: breast conserving surgery, MAS: mastectomy without breast reconstruction, A-BR: mastectomy with autologous breast reconstruction, I-BR: mastectomy with implant breast reconstruction, GP: general population. VAS: Visual Analogue Scale, 95% CI: 95% Confidence interval. Values in the same row and sub table not sharing the same superscript (^{a,b,c}) were significantly different at $p<0.05$ using the adjusted Wald test. Cells with no superscript were not included in the test. Tests assume equal variances.

Figure 1. Propensity-weighted EQ-5D-5L sub-scale per surgical treatment and weighted Dutch general population (GP)



BCS: breast conserving surgery, MAS: mastectomy without breast reconstruction, A-BR: mastectomy with autologous breast reconstruction, I-BR: mastectomy with implant breast reconstruction, GP: general population. Values in the same domain not sharing the same subscript were significantly different at p<0.05 using the adjusted Wald test.

Furthermore, for two EORTC-QLQ-C30 functioning scales, statistically significant differences were found. First, patients treated with I-BR reported a statistically significant higher mean 'Physical functioning' (87.97) than patients with BCS (84.53) or MAS (82.94), although comparable to A-BR (85.62). Second, I-BR patients reported a statistically significant higher mean 'Role functioning' (86.02) compared to patients treated with MAS (80.70). Within the 'Symptom Scales', statistically significant more favorable mean scores were found for BCS over MAS for 'Pain' (BCS: 15.41, MAS: 18.93;) and 'Financial problems' (BCS: 5.23, MAS: 8.22).

Based on the EORTC-QLQ-BR23 scores, mean 'Body image' was significantly higher for BCS-patients (BCS: 87.45; MAS: 80.49; A-BR: 82.28; I-BR: 82.35). BCS-patients also reported the lowest mean 'Arm symptoms' (BCS: 12.68; MAS: 17.12; A-BR: 18.18; I-BR: 16.82). In contrast, 'Breast symptoms' on average were more often reported by patients treated with BCS (13.45) than MAS (9.94) or A-BR (8.79). Patients with A-BR and I-BR reported the highest mean 'Sexual enjoyment' (A-BR: 64.24; I-BR: 63.80) compared to BCS or MAS (BCS: 57.03; MAS: 54.82).

For the Breast-Q scales, patients with A-BR reported the highest mean 'Satisfaction with Breasts' (A-BR: 71.29) compared to the other groups (BCS: 65.52; MAS: 60.65; I-BR: 59.39). Interestingly, 'Satisfaction with Breasts' for MAS and I-BR did not differ significantly. Mean 'Satisfaction with Outcome' and 'Satisfaction with Nipple' were significantly higher in A-BR than I-BR patients (A-BR: 75.75 vs, I-BR: 66.37; and A-BR: 63.03; I-BR: 54.96, respectively). MAS-patients reported the lowest mean 'Psychosocial well-being' (66.50) and 'Sexual well-being' (50.00).

Effect of complications on EQ-5D outcomes

A total of 96/615 (16%) of BCS, 112/507 (22%) of MAS, 138/330 (42%) of A-BR, and 140/419 (33%) of I-BR-patients reported to have experienced complications following surgery (unadjusted groups). After propensity-weighted adjustment, patients treated with either BCS, MAS, or A-BR who had experienced complications, showed statistically significant lower mean utilities than patients from the same groups who had not experienced complications (Table 3). Unadjusted results for the outcomes presented in this table can be found in appendix table 2. However, MAS patients without complications (0.818) reported means similar to A-BR-patients with complications (0.816) and I-BR-patients with complications (0.861). Mean EQ-5D scores of MAS-patients who previously had undergone a BR (e.g. failed BR) and who never had undergone a BR did not differ significantly from each other (p=0.943, results not shown).

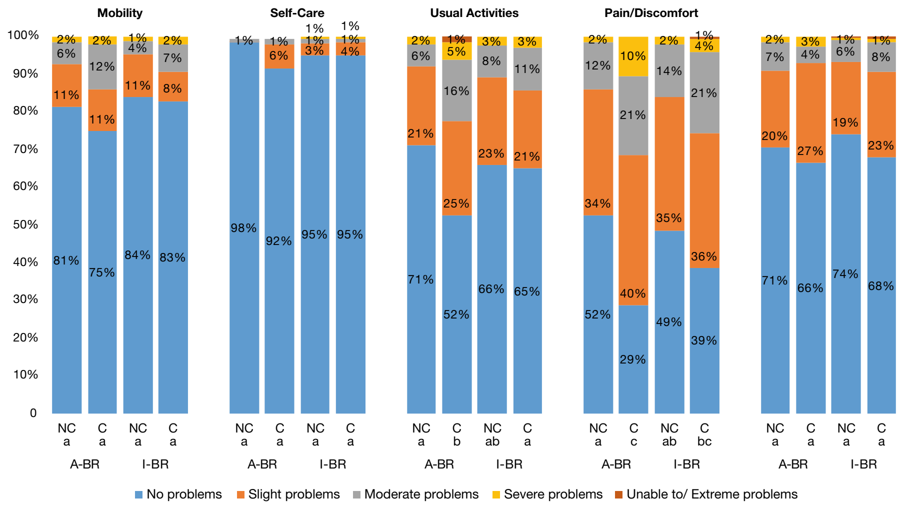
Table 3. Mean EQ-5D-5L utilities for 1871 breast cancer patients with or without surgical complications per treatment group and the Dutch general population after propensity-weighted adjustment

	Adjusted group				
	BCS	**MAS**	**A-BR**	**I-BR**	**GP**
Group size (n)	**434**	**386.3**	**178.6**	**295.5**	**N/A**
No complications	82.3%	75.0%	53.4%	68.4%	100%
Mean EQ-5D-5L utilities (CI)	0.859^{a} (0.844-0.875)	0.818^{b} (0.796-0.840)	0.878^{a} (0.854-0.902)	0.847^{a,b} (0.810-0.884)	0.833^{b} (0.812-0.854)
Complications	17.7%	25.0%	46.6%	31.6%	
Mean EQ-5D-5L utilities (CI)	0.771^{a} (0.729-0.812)	0.771^{a} (0.736-0.806)	0.816^{a,b} (0.780-0.853)	0.861^{b} (0.834-0.888)	N/A

BCS: breast conserving surgery, MAS: mastectomy without breast reconstruction, BR: breast reconstruction, A-BR: mastectomy with autologous BR, I-BR: mastectomy with implant BR, GP: general population. CI: 95% Confidence interval. Values in the same row and sub table not sharing the same superscript (^{a,b}) were significantly different at p<0.05 using the adjusted Wald test. Cells with no superscript were not included in the test. Tests assume equal variances.

For both BR groups, problems reported per EQ-5D domain were stratified by complications (Figure 2). A-BR patients with complications reported statistically significant more often problems for the 'Usual activities' and "Pain/Discomfort" domain than A-BR patients without complications.

Figure 2. EQ-5D-5L sub-scale contrasting A-BR and I-BR with or without surgical complication (unadjusted for propensity score)



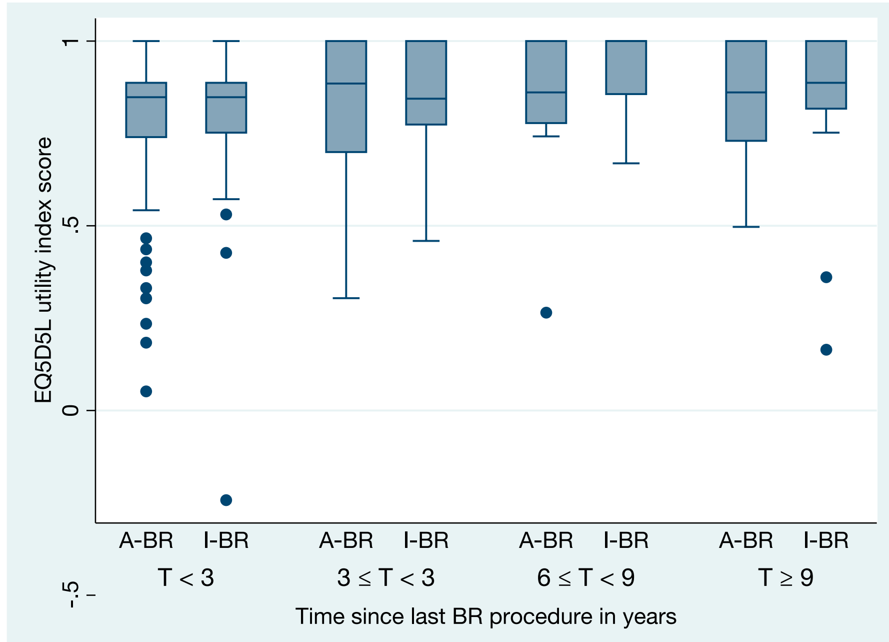
A-BR: mastectomy with autologous BR, I-BR: mastectomy with implant BR, GP: general population. C = surgical complications; NC = no surgical complications. Values in the same domain not sharing the same subscript were significantly different at p<0.05 using the Adjusted Wald test. Cells without subscript were not included in the test. Tests assume equal variances.

Figure 3 includes boxplots presenting timelines of the utilities for A-BR and I-BR patients who had experienced complications, unadjusted by propensity weighting. In the first three years after a complicated BR, a relatively large proportion of A-BR patients experienced a severe impact on HRQoL. This negative impact on HRQoL recovered with time for both treatment modalities. However, a larger proportion of I-BR patients seemed to recover up to the degree that they did not report problems on any of the EQ-5D dimensions within 6-9 years after the last BR surgery, compared to a much smaller portion of A-BR patients.

Discussion

This study aimed to compare HRQoL outcomes for four common surgical breast cancer treatment options (BSC, MAS, A-BR, I-BR) to improve the evidence and consequently decision-making about breast cancer surgery. We found that MAS-patients reported

Figure 3. EQ-5D-5L utilities over time in years (time between last BR and questionnaire) for breast cancer patients following breast reconstruction with complications



A-BR: mastectomy with autologous BR, I-BR: mastectomy with implant BR

the lowest mean HRQoL (EQ-5D) and functioning (EORTC-QLQ-C30). Based on the Breast-Q, A-BR-patients had statistically significant higher 'satisfaction with outcome' and 'satisfaction with breasts' and 'sexual well-being' scores than I-BR patients. Patients with complications (except for I-BR) reported statistically significant lower HRQoL (EQ-5D) than patients without complications; complications in A-BR patients resulted in a substantially lower HRQoL than in I-BR patients.

The results show the added value of breast conservation and reconstruction compared to MAS, however, the differences between BCS, I-BR, and A-BR were subtle. Indeed, we found many statistically significant differences, but given the high statistical power of our large study most of them were small. So, on average we found few clinically relevant differences between BCS, I-BR, and A-BR for the various HRQoL domains. However, the benefits of these subtle differences over a long time are a good reason to consider them in clinical decision-making, specifically when considering the effects of complications and the patients' attitude towards the risks of complications.

Only one other study that reported EQ-5D derived utilities for surgically-treated breast cancer patients receiving BR was found (Immediate IBR-patients, mean score: 0.83).[14] We found lower mean HRQoL scores reported by MAS-patients and benefits in some HRQoL domains for BCS-patients (higher 'Body Image' and more favorable 'Arm Symptom') over all other surgically treated groups, which confirms previously reported results.[15,32,20] The benefits of A-BR compared to I-BR (higher mean 'Satisfaction with Breasts/Outcome/Nipple', and 'Sexual Well-being') were also reported by Santosa et al.[22] However, in contrast, both the present study and Thorarinsson et al.[33] did not find statistically significant differences between A-BR and I-BR on either EQ-5D-5L or EORTC-QLQ outcomes. So, although the BREAST-Q results suggest that the patients' perception of their reconstructed breast(s) is favorable for A-BR over I-BR, this does not necessarily lead to better outcomes in terms of overall HRQoL.

The second aim was to assess the impact of complications after different surgical treatments. Indeed, if any clinically relevant differences were found,[34] they seemed to be related to complications. Specifically for A-BR, one should not ignore the impact of complications.[35] A-BR patients with complications (versus those without complications) had statistically significant lower mean utilities as measured with the EQ-5D, and more often had problems in the 'Usual activities' and 'Pain/Discomfort' domains. Also, mean scores recovered faster for I-BR patients than A-BR patients. Finally, a larger proportion of A-BR patients never recovered up to the degree that they did not report problems on any of the EQ-5D dimensions.

The faster recovery after complications of I-BR patients could explain why the utilities in patients with and without complications did not differ statistically. The symptoms and the longer lasting impact of complications in A-BR patients may be inherent to the type of complications associated with these procedures. More specifically, failure of an I-BR is often due to an infection, resulting in removal of the implant, later often followed by a new I-BR. Total flap failure following A-BR requires a new and additional donor-site, with its own donor-site issues and complication risks. Women experience BR (flap) failure as an emotionally very difficult life event,[36] although previous studies have shown that physical and mental health after a BR complication generally recover to normal levels after a period of time.[37,38]

By measuring HRQoL using multiple, validated PROMs in a large sample of patients following different types of breast cancer surgery, we were able to improve earlier, smaller and less consistent attempts to assess HRQoL in surgically-treated breast cancer patients. Our statistically significant results confirm the findings of studies mentioned previously,[15,20,22,32,35] thereby supporting the added value of breast conservation and reconstruction for breast cancer patients.

Furthermore, no predominant treatment option was found. This stresses the idea that all treatment options (which are physically feasible) should be considered for every patient. The ultimate treatment decision should be predominantly based on the patient's preferences, resulting in the alignment of the favorable assets (or domain scores) of each procedure and the patient's goals and expectations with the expected final result of each procedure as well as their attitudes towards complication risks. Although we have investigated decision-making in a previous study in a similar cohort of patients[39], it would have been interesting to have insight in the treatment rationale for the current patient cohort.

This study demonstrates the utilization of the unique assets of the EQ-5D, a 'preference-based', standardized generic measure of health status which is suitable for a wide comparison of treatment options.[40,41] A benefit of this preference-based HRQoL measure compared to commonly applied 'non-preference-based' measures like the EORTC and Breast-Q is that its outcomes can be aggregated over time and, after multiplication with survival time, provides Quality Adjusted Life Years (QALYs).[41] The EQ-5D utilities can be related to the time period of each health state, and can therefore combine the 'utility' of the advantages and disadvantages, such as complications of surgical procedures. Note that our data were not able to fully solve the question how the utility of the benefits of a surgical procedure relates to the disutility of complications, as this requires longitudinal data to represent the EQ-5D values and the time lived with or without a given complication. Nevertheless, the present data can still provide insights in the trade-off between benefits and complications of the different surgical procedures.

Of further importance is that previous studies have not yet described 'utilities' for the complete range of breast cancer surgery options. This currently complicates the implementation of health economics and reimbursement decision-making. Clinical treatment value should be related to healthcare costs, which is the ultimate goal towards creating value-based health care.[42] In our subsequent study, we will relate costs to the outcomes we found in the present study.

Some limitations are relevant in the interpretation of our results. First, although propensity-weighted adjustment was employed to minimize the effects of bias caused by including patients from an observational cohort, one cannot exclude that relevant variables may still have influenced the results of our study.[43] For instance, surgical treatment selection might be based on severity of comorbidities or performance status, which were both not available in our data. Non-response bias could have been induced by socioeconomic and procedure-related differences, as described by Berlin et al.[44] Besides, surveys introduce a certain arbitrariness, as patients might understand or interpret questions or experiences other than intended.

We conclude that HRQoL of MAS-patients was often the lowest, supporting the added value of breast conservation and reconstruction in breast cancer patients. Furthermore, we found that each surgical procedure has subtle favorable assets, the most notable related to complications: a complication in A-BR patients resulted in a substantially lower HRQoL than in I-BR patients and MAS-patients without complications had similar or lower mean EQ-5D scores to A-BR or I-BR patients with complications. This could support a discussion about the alignment of the patient's goals, expectations and attitudes towards complication risks with the expected final result of each procedure.

Acknowledgements

The authors thank all women who participated in this study.

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Appendix

Table 1. Mean patient-reported quality of life scores of 1871 breast cancer patients per surgical treatment and the Dutch general population, before (left) and after (right) propensity-weighted adjustment

	Unweighted groups					Propensity weighted groups				
	BCS (95% CI)	MAS (95% CI)	A-BR (95% CI)	I-BR (95% CI)	GP (95% CI)	BCS (95% CI)	MAS (95% CI)	A-BR (95% CI)	I-BR (95% CI)	GP (95% CI)
Group size (n)	**615**	**507**	**330**	**419**	**505**	**434**	**386.3**	**178.6**	**295.5**	**N/A**
EQ-5D-5L										
Utilities	0.854[a] (0.840-0.868)	0.784[b] (0.769-0.800)	0.837[a] (0.818-0.856)	0.856[a] (0.839-0.873)	0.856[a] (0.841-0.872)	0.844[a] (0.829-0.859)	0.805[b] (0.787-0.823)	0.849[a] (0.828-0.871)	0.850[a] (0.823-0.877)	0.833[a] (0.812-0.854)
VAS Score	78.60[a] (77.22-79.22)	74.59[b] (73.09-76.10)	78.47[a] (76.59-80.34)	78.34[a] (76.69-80.01)	80.27[a] (78.75-81.78)	77.76[a] (76.02-79.51)	76.48[a] (74.75-78.22)	79.24[a] (76.76-81.72)	77.58[a] (75.52-79-65)	78.88[a] (77.08-80.69)
EORTC-QLQ-C30										
Global Health Status	80.89[a] (79.52-82.27)	77.98[b] (76.3-79.66)	80.86[a,b] (78.94-82.78)	80.42[a,b] (78.75-82.08)	N/A	80.00[a] (78.26-81.75)	79.01[a] (77.14-80.87)	81.38[a] (79.22-83.54)	80.16[a] (78.07-82.25)	N/A
<u>Function scales:</u>										
Physical function	85.07[a] (83.75-86.4)	79.86[c] (78.14-81.57)	86.66[a,b] (84.86-88.46)	89.15[b] (87.82-90.49)	N/A	84.53[a] (83.02-86.04)	82.94[a] (81.32-84.55)	85.62[a,b] (83.30-87.85)	87.97[b] (85.63-90.31)	N/A
Role function	85.29[a] (83.5-87.07)	77.96[b] (75.7-80.23)	84.09[a] (81.57-86.61)	86.04[a] (83.95-88.14)	N/A	84.35[a] (82.34-86.36)	80.70[b] (80.84-87.19)	84.02[a,b] (82.82-89.22)	86.02[a] (82.82-89.22)	N/A
Emotional function	85.51[a] (84.01-87.02)	83.33[a] (81.59-85.08)	85.63[a] (83.49-87.77)	84.65[a] (82.63-86.66)	N/A	85.36[a] (83.36-87.18)	83.84[a] (81.90-85.78)	87.00[a] (84.47-89.51)	85.04[a] (82.40-87.67)	N/A
Cognitive function	85.72[a] (84.14-87.3)	84.26[a] (82.43-86.08)	82.02[a] (79.73-84.31)	83.89[a] (81.73-86.05)	N/A	84.14[a] (82.21-86.06)	84.32[a] (82.32-86.31)	83.67[a] (80.53-86.82)	84.97[a] (82.29-87.65)	N/A
Social function	89.86[a] (88.38-91.35)	86.00[b] (84.08-87.92)	86.16[a,b] (83.91-88.41)	86.69[a,b] (84.62-88.76)	N/A	88.82[a] (87.01-90.63)	86.94[a] (87.01-90.63)	88.02[a] (85.54-90.50)	87.48[a] (84.40-90.55)	N/A
<u>Symptom scales:</u>										
Fatigue	21.17[a] (19.38-22.97)	24.59[a] (22.46-26.73)	23.47[a] (21.06-25.87)	20.81[a] (18.61-23.01)	N/A	21.82[a] (19.77-23.87)	22.54[a] (20.30-24.77)	22.39[a] (19.27-25.51)	20.21[a] (17.47-22.94)	N/A
Nausea and vomiting	2.98[a] (2.27-3.69)	3.62[a] (2.65-4.6)	2.88[a] (1.9-3.86)	3.39[a] (2.3-4.48)	N/A	2.72[a] (1.98-3.46)	3.31[a] (2.25-4.38)	2.83[a] (1.76-3.90)	3.35[a] (1.40-5.30)	N/A
Pain	14.99[a] (13.3-16.68)	20.16[b] (18.02-22.3)	16.72[a,b] (14.35-19.08)	15.95[a] (13.73-18.17)	N/A	15.41[a] (13.56-17.25)	18.93[b] (16.53-21.32)	17.18[a,b] (14.07-20.28)	15.89[a,b] 12.87-18.90)	N/A
Dyspnea	13.44[a] (11.67-15.22)	14.56[a] (12.44-16.68)	12.46[a,b] (10.13-14.8)	9.65[b] (7.81-11.49)	N/A	14.28[a] (12.18-16.39)	12.22[a] (10.12-14.31)	13.39[a] (9.75-17.03)	10.82[a] (8.06-13.59)	N/A
Insomnia	22.93[a] (20.68-25.17)	24.44[a] (21.88-27)	23.23[a] (20.09-26.38)	25.04[a] (22.21-27.87)	N/A	22.76[a] (20.09-25.44)	22.69[a] (19.93-25.44)	20.37[a] (16.87-23.87)	25.11[a] (21.10-29.11)	N/A
Appetite loss	6.02[a] (4.7-7.33)	5.34[a] (3.88-6.79)	3.94[a] (2.56-5.32)	3.75[a] (2.36-5.13)	N/A	5.87[a] (4.45-7.30)	4.08[a] (2.90-5.26)	3.81[a] (2.25-5.37)	3.90[a] (1.78-6.03)	N/A
Constipation	6.78[a] (5.45-8.1)	7.85[a] (6.23-9.48)	8.59[a] (6.31-10.86)	6.38[a] (4.73-8.03)	N/A	6.98[a] (5.38-8.59)	7.07[a] (5.34-8.79)	7.96[a] (5.29-10.63)	5.29[a] (3.80-6.78)	N/A
Diarrhea	4.82[a] (3.65-6)	4.82[a] (3.57-6.07)	4.14[a] (2.6-5.68)	4.70[a] (3.24-6.17)	N/A	4.81[a] (3.52-6.10)	4.43[a] (3.14-5.72)	3.24[a] (1.96-4.51)	4.65[a] (3.11-6.19)	N/A
Financial problems	5.04[a] (3.86-6.22)	7.51[a,c] (5.88-9.14)	11.92[b] (9.27-14.57)	8.79[b,c] (6.7-10.89)	N/A	5.23[a] (3.77-6.69)	8.22[b] (6.16-10.28)	12.30[b] (8.41-16.19)	7.71[a,b] (5.21-10.22)	N/A

(continued)

Table 1. Continued

	Unweighted groups					Propensity weighted groups				
	BCS (95% CI)	MAS (95% CI)	A-BR (95% CI)	I-BR (95% CI)	GP (95% CI)	BCS (95% CI)	MAS (95% CI)	A-BR (95% CI)	I-BR (95% CI)	GP (95% CI)
Group size (n)	**615**	**507**	**330**	**419**	**505**	**434**	**386.3**	**178.6**	**295.5**	**N/A**
EORTC-QLQ-BR23										
Function scales:										
Body image	89.19^{a} (87.72-90.67)	79.43^{b} (76.51-82.35)	80.65^{b} (78.3-83)	80.10^{b} (78.07-82.14)	N/A	87.45^{a} (85.45-89.45)	80.49^{b} (78.24-82.74)	82.28^{b} (79.01-85.55)	82.35^{b} (79.83-84.88)	N/A
Sexual functioning	28.48^{a,c} (26.34-30.61)	31.14^{a,b} (28.3-33.97)	35.71^{b} (32.91-38.5)	25.13^{c} (22.71-27.54)	N/A	27.90^{a} (25.23-30.58)	27.51^{a} (24.80-30.22)	31.95^{a,b} (28.02-35-89)	33.35^{b} (29.99-36.72)	N/A
Sexual enjoyment	55.73^{a,c} (52.42-59.03)	61.93^{a,b} (57.5-66.36)	65.04^{b} (61.71-68.37)	53.80^{c} (50.19-57.42)	N/A	57.03^{a} (53.03-61.02)	54.82^{a} (51.07-58.57)	64.24^{b} (59.27-69.21)	63.80^{b} (60.06-67.54)	N/A
Future perspective	75.57^{a} (73.61-77.54)	71.97^{a,b} (68.97-74.97)	73.18^{a,b} (70.67-75.69)	71.38^{b} (68.92-73.84)	N/A	74.51^{a} (72.17-76.85)	71.93^{a} (69.15-74.71)	76.14^{a} (72.34-79.95)	75.03^{a} (72.21-77.85)	N/A
Symptom scales:										
Systemic therapy side-effects	12.35^{a} (11.35-13.35)	15.20^{b} (13.64-16.75)	14.02^{a,b} (12.66-15.38)	13.22^{a,b} (12.06-14.38)	N/A	12.60^{a} (11.57-13.64)	12.74^{a} (11.49-13.99)	14.41^{a} (12.41-16.40)	13.79^{a} (12.08-15.50)	N/A
Breast symptoms	12.71^{a} (11.41-14.02)	8.77^{b} (7.4-10.13)	9.68^{b} (8.18-11.18)	10.69^{a,b} (9.33-12.05)	N/A	13.45^{a} (11.80-15.11)	9.94^{b} (8.60-11.28)	8.79^{b} (6.88-10.71)	10.82^{a,b} (8.36-13.27)	N/A
Arm symptoms	11.31^{a} (9.91-12.71)	18.56^{b} (16.29-20.84)	15.38^{b} (13.41-17.36)	17.57^{b} (15.77-19.38)	N/A	12.68^{a} (11.02-14.34)	17.12^{b} (15.12-19.12)	18.18^{b} (14.94-21.41)	16.82^{b} (13.60-20.03)	N/A
Hair loss	3.93^{a} (2.77-5.1)	7.26^{b} (5.05-9.47)	5.95^{a,b} (4.06-7.83)	5.59^{a,b} (3.98-7.2)	N/A	4.25^{a} (2.78-5.71)	4.86^{a} (3.37-6.35)	6.50^{a} (4.02-8.98)	5.47^{a} (3.58-7.37)	N/A
BREAST-Q										
Satisfaction with Breasts	67.84^{a} (66.15-69.52)	60.22^{b} (58.64-61.81)	70.74^{a} (68.67-72.81)	59.53^{b} (57.9-61.17)	N/A	65.52^{a} (63.43-67.61)	60.65^{b} (58.79-62.51)	71.29^{c} (68.66-73.92)	59.39^{b} (57.18-61.60)	N/A
Satisfaction with Outcome	N/A	N/A	75.39^{a} (72.81-77.96)	66.35^{b} (64.18-68.53)	N/A	N/A	N/A	75.75^{a} (72.52-78.99)	66.37^{b} (63.66-69.08)	N/A
Psychosocial Well-being	75.31^{a} (73.61-77.01)	66.15^{c} (64.58-67.71)	74.09^{a,b} (71.97-76.21)	71.11^{b} (69.19-73.03)	N/A	73.77^{a} (71.70-75.83)	66.50^{b} (64.68-68.32)	75.78^{a,c} (72.94-78.63)	71.60^{a} (69.30-73.90)	N/A
Sexual Well-being	64.39^{a} (62.20-66.57)	48.31^{d} (45.96-50.66)	61.58^{b} (58.79-64.38)	56.82^{c} (54.59-59.06)	N/A	62.70^{a} (59.92-65.48)	50.00^{b} (47.44-52.55)	63.33^{a} (58.91-67.75)	56.38^{c} (52.88-59.88)	N/A
Physical Well-being: Chest	68.90^{a} (67.45-70.36)	73.41^{b} (71.84-74.97)	74.95^{a} (73.15-76.74)	72.75^{b} (71.06-74.45)	N/A	67.39^{a} (65.17-69.61)	73.47^{b} (71.78-75.16)	75.81^{b,c} (73.56-78.06)	72.64^{b} (70.61-74.66)	N/A
Physical Well-being: Abdomen	N/A	N/A	78.25 (75.95-80.56)	N/A	N/A	N/A	N/A	75.81 (73.56-78.06)	N/A	N/A
Satisfaction Nipple	N/A	N/A	63.63^{a} (60.03-67.23)	55.28^{b} (50.66-59.89)	N/A	N/A	N/A	63.03^{a} (58.82-67.25)	54.96^{b} (49.38-60.54)	N/A

BCS: breast conserving surgery,
MAS: mastectomy without breast reconstruction,
A-BR: mastectomy with autologous breast reconstruction,
I-BR: mastectomy with implant breast reconstruction,
GP: general population.
VAS: Visual Analogue Scale,
95% CI: 95% Confidence interval.

Values in the same row and subtable not sharing the same superscript (^{a,b}) were significantly different at $p<0.05$ using the adjusted Wald test. Cells with no superscript were not included in the test. Tests assume equal variances.

Table 2. Mean EQ-5D-5L utilities for 1871 breast cancer patients with or without surgical complications per treatment group and the Dutch general population, before (left) and after (right) propensity-weighted adjustment

	Unadjusted group					Adjusted group				
	BCS	MAS	A-BR	I-BR	GP	BCS	MAS	A-BR	I-BR	GP
Group size (n)	615	507	330	419	505	434	386.3	178.6	295.5	N/A
No complications	84.5%	77.9%	58.2%	66.6%	100%	82.3%	75.0%	53.4%	68.4%	100%
Mean EQ-5D-5L utilities (CI)	0.869[a] (0.854-0.883)	0.800[b] (0.781-0.818)	0.872[a] (0.848-0.89)	0.868[a] (0.848-0.887)	0.856[a] (0.842-0.871)	0.859[a] (0.844-0.875)	0.818[b] (0.796-0.840)	0.878[a] (0.854-0.902)	0.847[a,b] (0.810-0.884)	0.833[b] (0.812-0.854)
Complications	15.6%	22.1%	41.8%	33.4%	N/A	17.7%	25.0%	46.6%	31.6%	
Mean EQ-5D-5L utilities (CI)	0.770[a] (0.731-0.809)	0.753[a] (0.717-0.789)	0.791[a] (0.759-0.823)	0.839[b] (0.807-0.872)	N/A	0.771[a] (0.729-0.812)	0.771[a] (0.736-0.806)	0.816[a,b] (0.780-0.853)	0.861[b] (0.834-0.888)	N/A

BCS: breast conserving surgery,
MAS: mastectomy without breast reconstruction,
BR: breast reconstruction,
A-BR: mastectomy with autologous BR,
I-BR: mastectomy with implant BR,
GP: general population.
CI: 95% Confidence interval.

Values in the same row and subtable not sharing the same superscript ([a,b]) were significantly different at $p<0.05$ using the adjusted Wald test. Cells with no superscript were not included in the test. Tests assume equal variances.

Chapter 4

Cost-Utility Analysis of Four Common Surgical Treatment Pathways for Breast Cancer

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Abstract

Background
The aim was to evaluate the cost-utility of four common surgical treatment pathways for breast cancer: mastectomy, breast-conserving therapy (BCT), implant breast reconstruction (BR) and autologous-BR.

Methods
Patient-level healthcare consumption data and results of a large quality of life (QoL) study from five Dutch hospitals were combined. The cost-effectiveness was assessed in terms of incremental costs and quality adjusted life years (QALYs) over a 10-year follow-up period. Costs were assessed from a healthcare provider perspective.

Results
BCT resulted in comparable QoL with lower costs compared to implant-BR and autologous-BR and showed better QoL with higher costs than mastectomy (€17,246/QALY). QoL outcomes and costs of especially autologous-BR were affected by the relatively high occurrence of complications. If reconstruction following mastectomy was performed, implant-BR was more cost-effective than autologous-BR.

Conclusions
The occurrence of complications had a substantial effect on costs and QoL outcomes of different surgical pathways for breast cancer. When this was taken into account, BCT was most the cost-effective treatment. Even with higher costs and a higher risk of complications, implant-BR and autologous-BR remained cost-effective over mastectomy. This pleas for adapting surgical pathways to individual patient preferences in the trade-off between the risks of complications and expected outcomes.

Introduction

One in eight women will develop breast cancer in her lifetime.[1-3] Surgical treatment pathways for early-stage breast cancer patients consist of either breast-conserving surgery (BCS) or mastectomy.[4, 5] The advantage of BCS over mastectomy is preservation of the breast contour, thereby optimizing cosmetic outcome of the affected breast.[4] However, BCS needs to be followed by adjuvant radiotherapy, known as breast-conserving therapy (BCT), to reach oncological outcomes similar to mastectomy.[6-8] Some patients therefore prefer mastectomy because of concerns about radiation effects or disease recurrence in case of BCT[9] or may require mastectomy based on contra-indications for BCS or radiotherapy.[4, 5]

Because loss of a breast may negatively affect psychological health, body image, and sexual function,[10, 11] (inter)national guidelines recommend that the possibility of postmastectomy breast reconstruction (BR) should be discussed with every patient with an indication for mastectomy.[4, 5, 12] Multiple BR options are available, either using autologous tissue with a pedicled or free flap (autologous-BR) or breast implants (implant-BR), varying in costs, timing, duration, complication rates, and cosmetic results.[10, 13, 14] Postmastectomy BR aims to improve the patient's well-being and quality of life (QoL),[10, 11, 13] but patients opting for BR also have a risk of complications,[15-18] reconstruction failure,[15, 16] or disappointing (cosmetic) outcomes.[10] Consequently, shared decision-making between physician and patient on which surgical treatment is preferred comprises a complex trade-off between risks and outcomes.

Beside considering risks and benefits for the patient in choosing treatment modalities, different treatment pathways have different costs. In the current times of scarcity of healthcare budgets, it is relevant to know which intervention provides the most benefit (i.e., health) per dollar or euro. This is not only relevant when choosing between surgical options for breast cancer, but this is also relevant when the reimbursement of these surgical options is in competition with other allocations of the healthcare budget. In that respect, BR is in a vulnerable position, as it aims at improving quality of life rather than survival. Evidence that a given surgical treatment has a favorable cost-effectiveness will help to strengthen its position if scarcity in healthcare budgets emerge.

Evidence about the cost-effectiveness of aforementioned common surgical treatment pathways for breast cancer compared to other allocations of budget in healthcare is only meaningful if it is possible to directly compare the outcomes of these surgical treatment pathways with other medical interventions. The formal way to do so is to perform a 'cost-utility analysis', as indicated in literature and guidelines on health economics.[19-23] This is a special case of cost-effectiveness analysis where QoL outcomes are defined in generic terms, Quality Adjusted Life Years (QALYs), so that different interventions can be directly compared. State-of-the-art QALY analysis uses specific validated questionnaires such as the EQ-5D to estimate QALYs.[20, 23-25]

A recent meta-analysis compared 16 studies which have investigated the cost-effectiveness of DIEP-flap and implant-based BR techniques.[26] The authors concluded that DIEP-flap BR may be more cost-effective and yields superior patient-reported outcomes. However, the quality of the included studies was considered poor, showing high degrees of bias. Moreover, in a large cross-sectional study by Kouwenberg et.al., after controlling for differences in pre-treatment patient characteristics, this superiority of autologous-BR over implant-BR was not reproducible using a generic QALY measure.[11] No statistically significant differences in EQ-5D outcomes/utilities could be found between patients following BCT, implant-BR and autologous-BR, but all three patient groups had significantly better outcomes/utilities than mastectomy patients.[11]

The aim of the present study was to compare the cost-effectiveness of the four most common surgical breast cancer treatment pathways (mastectomy without BR, BCT, mastectomy followed by implant-BR, and mastectomy followed by autologous-BR) using state-of-the-art methods.

Methods

Overview

The purpose of this analysis was to compare four common surgical treatment pathways (mastectomy, BCT, implant-BR and autologous-BR) for breast cancer patients using real patient-level healthcare consumption data for all patients who had undergone surgical breast cancer treatment in four general and one academic hospital in the Netherlands between January 1st, 2005 and January 1st, 2017. The four treatment pathways were compared on their relative costs of major care categories (surgical interventions, radiotherapy, outpatient visits, admission days and diagnostics related resources), costs of complications during the treatment pathway and QoL on an intention-to-treat basis. From these figures, the cost-effectiveness was assessed in terms of incremental costs and QALYs over a 10-year follow-up period. A 10-year period was chosen, as costs for BR are incurred over a longer period of time. Costs were assessed from a healthcare provider perspective based on Dutch unit costs. However, the healthcare provider perspective does not cover all societal costs. For instance, productivity loss (work) and small out-of-pocket costs, like travel costs were not included. This was because in this investigation it was not possible to collect such data from hospital registers, and retrospectively collecting such data retrospectively over a 10-year period is cumbersome. Quality of life data of the relevant health states was available from previous research of our group.[11] A complete follow-up period of 10 years was not available for all patients because of the continued inclusion in the cohort, which led to right censoring of the cost and health utility data . These missing data were addressed using a Multiple Imputation technique that accounts for uncertainty in the respective treatment arm.[27] Furthermore, three scenario sensitivity analyses were performed to explore the effects of different scenarios regarding 1) OR costs, 2) re-operation rates for implant-BR and 3) complication rates for autologous-BR.

The Medical Ethics Committee of the Erasmus MC reviewed and approved the study protocol (MEC-2015-273).

Defining the cohort for analysis

This multicenter observational cohort study included all patients who had undergone surgical breast cancer treatment in one of the participating hospitals in the period between January 1st, 2005 and January 1st, 2017. Cohorts were defined on an intention-to-treat basis where patients had either undergone BCS or mastectomy. Medical intervention billing coding was used to identify the procedure a patient had received and to which cohort the patient belonged.

Because an intention-to-treat design was used, if postmastectomy BR had been performed, the type of the first BR procedure defined the cohort. For example, if a patient initially had undergone an implant-BR, but due to complications this BR was converted to an autologous-BR, this patient remained in the implant-BR cohort. All autologous-BR patients had undergone a breast reconstruction using free tissue transfer (almost exclusively DIEP-flaps). Patients who had undergone novel and more rare types of BR as their first BR (such as a latissimus dorsi or pedicled TRAM-flap) were excluded from the analyses, as they were considered out of the scope of the current cost-effectiveness analysis (CEA).

In the Netherlands, autologous-BR is performed in a limited number of hospitals. This means that a large proportion of patients had received their oncological breast cancer treatment at a different hospital than one of the participating hospitals and that they had been referred to receive their autologous-BR at a later stage in one of the participating centers. Consequently, the data on the oncological surgery part of their treatment was not available for these patients. Multiple imputation techniques were therefore used to address the missing surgery data.[27, 42] These patients by definition had a delayed BR and for them the mean time between mastectomy and autologous-BR was used, which could be calculated for cases that had received their oncological surgery treatment at one of the participating centers.

Resource use and costs

Costs of Surgical interventions

A costing model used previously for a costing-study by Damen et al. was further developed and updated to reflect 2018 prices for the current study.[31, 43] Surgical interventions were expected to be one of the main cost drivers. For this reason, we put emphasis on precise calculation of these costs. For instance, the costs for an operating room (OR) were calculated on a per minute basis for the surgeon, anesthesiologist, supporting personnel, and OR-related costs. In addition, a base fee for the OR, and breast implant costs, if used, were also added. The hospital operation registration system was used to score which surgical procedures were performed, who performed the operation, as well as details on the start and end of the operation.

After surgery, as time goes by, it becomes increasingly complicated to attribute a given medical procedure to a complication of the surgical procedure of interest. This is impeded by the often-compendious labelling of events in the hospital registers. Therefore, the occurrence of a surgical complication that required reoperation was defined as the occurrence of an additional operative procedure within 60 days. Even though long-term complications were not formally identified, the costs incurred by such complications were included in the analysis, as all relevant treatment costs during the follow-up period were included.

Costs of Radiotherapy

Because radiotherapeutic treatment in the Netherlands is centralized in a limited number of hospitals, some patients had received their radiotherapeutic treatment outside the group of five hospitals in this investigation. Therefore, costs data related to radiotherapeutic treatment could not be obtained for all patients from the hospital administrative records of four of the five participating hospitals. Consequently, radiotherapeutic resource use per patient was obtained from the Netherlands Cancer Registry upon request.[44] Unit costs for radiotherapeutic treatment were calculated as the weighted average of the resource use and reference costs for BC patients in the hospital for which these records were available. These unit costs were subsequently multiplied by the resource use as registered in the Netherlands Cancer Registry. For comparability purposes this method was employed for all patients. All BCS patients were assumed to have received radiotherapy, which is standard of care in the Netherlands.

Other Costs

Use of other cost resources were collected from the hospital administrative records. Three main categories of resources were defined: outpatient related resources, admission related resources and diagnostics related resources. The total costs for each patient were calculated by multiplying the resource use by the appropriate unit costs, standardized to 2018 prices. The Statistics Netherlands (CBS) inflation tool was used to adjust prices of all resources, also of the surgical interventions and radiotherapy.[43] Multiple sources were used to obtain unit costs, in order of preference: reference costs for medical resources as published by the National Health Care Institute (Zorginstituut Nederland), national costs guideline for diagnostic procedures, cost prices provided by business information departments of respective hospitals, reimbursement fees of healthcare insurers.[23, 24]

Health outcomes

Patients' health states were defined on a per year basis based on the last operation they had undergone. Four health states were defined: mastectomy, BCT, implant-BR and

autologous-BR. In order to be able to associate these four health states with QALY values, the EQ-5D-5L outcomes of our previous study were used, which were controlled for differences in pre-treatment patient characteristics.[11] The utility values and their 95% confidence intervals that were used from this study were respectively, BCT 0.844 (CI: 0.829-0.859), mastectomy 0.805 (CI: 0.787-0.823), autologous-BR 0.849 (CI: 0.828-0.871), implant-BR 0.850 (CI: 0.823-0.877).[11] The QALY weights provided by the EQ-5D-5L where based on Dutch societal values.[45] To account for the variance in health utility outcomes over time and between patients, all health state utilities were drawn randomly from a beta distribution of health state utility values specific for the respective treatment group.

Missing data and censoring

A complete follow-up period of 10 years was not available for all patients because of the continued inclusion in the cohort. This leads to right censoring of the cost and health utility data for these patients. The missing data were addressed according to the guideline "A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomized Controlled Trials" by Faria et.al. using multiple imputation with chained equations using predictive mean matching (MI-PMM) from within the respective treatment arm.[27] This approach recognizes uncertainty associated with missing data and subsequent estimated parameters in the imputation model and is also appropriate for cost and utility data that is non-normally distributed.[27, 42] To facilitate MI-PMM, costs categories and health state data were aggregated in incremental segments of 1-year follow-up after which the imputation procedure was performed using the ICE program in Stata 14 on Mac OSX. Fifty imputation datasets were created with a random seed of 10.

Cost-effectiveness and sensitivity analysis

Total costs for each cost category, total costs for both the surgical oncology and plastic surgery departments, overall total costs and total QALYs aggregated (over time) were calculated for each patient in the imputed datasets. Costs and QALYs were discounted with a rate of 4% and 1.5% per year, respectively, in accordance with the national guideline on CEA.[24] Discounting accounts for the economic theory that effects and costs become of less value to an individual the further away in the future they are.[20] The main measure of cost-effectiveness is the incremental cost-effectiveness ratio (ICER), calculated as the difference in mean costs per patient divided by the difference in mean QALYs per patient over the 10-year period. In addition to a full-incremental analysis in which all available options were compared to another, also pairwise comparisons were performed.

The MIM2 program in Stata was used for basic analysis of the imputed datasets using Rubin's rules.[46] Furthermore, three scenario sensitivity analyses were performed: 1) 20% higher and lower OR costs were investigated to illustrate the effects of any differences in this main costs driver. 2) A scenario which assumed that all implant-BR patients needed to undergo one re-operation in year 10 for implant replacement and for which all associated additional costs were taken into account. The reason for investigating this scenario was that implant-BR is associated with a relatively high risk of additional operations in the long-term due to for example capsular contracture or implant rupture.[26, 40, 47] The costs of these additional operations have often been mentioned as closing the costs gap between autologous-BR and implant-BR, which would eventually lead to break-even costs in the long-term.[34] 3) The effects of a reduction of the complication rate of autologous-BR on QoL as well as on costs were investigated in a weighted average fashion. This scenario illustrates possible effects of differences and future improvements in quality of care.

Results

In total, 3706 mastectomy, 3553 BCT, 621 implant-BR and 513 autologous-BR patients were included in the present analysis. The patient characteristics of the different intention-to-treat treatment pathways are listed in Table 1. Most notable is the relatively higher age in the mastectomy and BCT cohorts compared to the BR cohorts.

Table 1. Characteristics of 8393 breast cancer patients by surgical treatment pathway

Mean (SD)	MAS	BCT	I-BR	A-BR
N	3706 (44.2%)	3553 (42.3%)	621 (7.4%)	513 (6.1%)
Age at BC Dx	62.9 (13.9)	59.2 (11.4)	49.2 (10.6)	48.2 (10.6)
Follow up in months	83.0 (52.1)	91.8 (49.9)	96.4 (48.8)	86.9 (50.8)
Immediate BR	NA	NA	55.4%	0%
BCS Conversion <6m	NA	1.2%	NA	NA
BR Conversion	NA	NA	8.9%	0.8%
Reoperations within 60 days				
0	77.4%	75.5%	58.0%	75.1%
1	20.2%	21.5%	31.9%	15.0%
2-3	2.4%	2.8%	9.3%	8.4%
>3	0.1%	0.2%	0.8%	1.6%
Reoperations within 45 days				
0	78.5%	77.0%	60.6%	75.6%
1	19.4%	20.6%	30.1%	14.8%
2-3	2.0%	2.1%	8.7%	8.2%
>3	0.1%	0.2%	0.6%	1.4%
Mean number admission days	4.8	3.3	8.8	9.7
Hospital type				
General	83%	85.6%	83.6%	9.0%
Academic	17%	14.4%	16.4%	91.0%

MAS: mastectomy without breast reconstruction, BCT: breast conserving therapy, I-BR: mastectomy with implant breast reconstruction, A-BR: mastectomy with autologous breast reconstruction.

Cost-analysis and cost-effectiveness

Mean costs per cost category per treatment pathway, which are further addressed in the next paragraphs, are shown in Table 2 and Figure 1. Figure 2 shows the histograms of the total incurred costs per patient for each of the different treatment pathways and provides more insight in the variability and distribution of the costs among the different treatment pathways. The higher peaks and narrower distribution of the mastectomy and BCT groups show that there was less variability in the total costs of these treatments compared to implant-BR and autologous-BR. One autologous-BR patient had incurred very high costs (€401,953) in her treatment pathway, due to a severe, chronic auto-inflammatory syndrome. This outlier is not shown in Figure 2.

Table 2. Cost-effectiveness outcomes over a 10-year period by surgical treatment pathway

	MAS	BCT	I-BR	A-BR
Mean costs				
Oncologic Surgery				
Total	€ 9 066	€ 8 543	€ 9 977	€ 10 075
Discounted Total	€ 8 749	€ 8 164	€ 9 610	€ 9 638
Subtotals:				
Operation	€ 2 479	€ 2 285	€ 2 804	€ 3 677
Non-OR:	€ 6 588	€ 6 258	€ 7 173	€ 6 397
First 3 years Outpatient	€ 1 206	€ 1 125	€ 1 396	€ 1 712
Admission	€ 2 117	€ 1 301	€ 2 059	€ 1 452
Diagnostics	€ 2 049	€ 2 329	€ 2 296	€ 2 027
Plastic Surgery				
Total	€ 486	€ 1 093	€ 9 578	€ 15 004
Discounted Total	€ 441	€ 991	€ 8 843	€ 13 728
Subtotals:				
Operation	€ 104	€ 436	€ 5 261	€ 7 669
Non-OR:	€ 383	€ 657	€ 4 317	€ 7 335
First 8 years Outpatient	€ 219	€ 314	€ 1 724	€ 2 174
Admission	€ 101	€ 247	€ 2 014	€ 4 459
Diagnostics	€ 28	€ 47	€ 193	€ 602
Radiotherapy	€ 1 743	€ 7 606	€ 823	€ 2 480
Overall undiscounted total	€ 11 296	€ 17 242	€ 20 377	€ 27 559
Overall discounted total	€ 10 933	€ 16 761	€ 19 275	€ 25 846
Undiscounted QALY's accrued	8.05	8.41	8.40	8.41
Discounted QALY's accrued	7.53	7.87	7.85	7.85
Pairwise: Incremental cost-effectiveness ratio, undicsounted (€/QALY)				
vs MAS	NA	16 521	28 406	51 715
vs BCT			Dom. by BCT	16227 856
vs I-BR				537 933
Pairwise: Incremental cost-effectiveness ratio, discounted (€/QALY)				
vs MAS	NA	17 246	26 093	47 422
vs BCT			Dom. by BCT	Dom. by BCT
vs I-BR				Dom. by I-BR

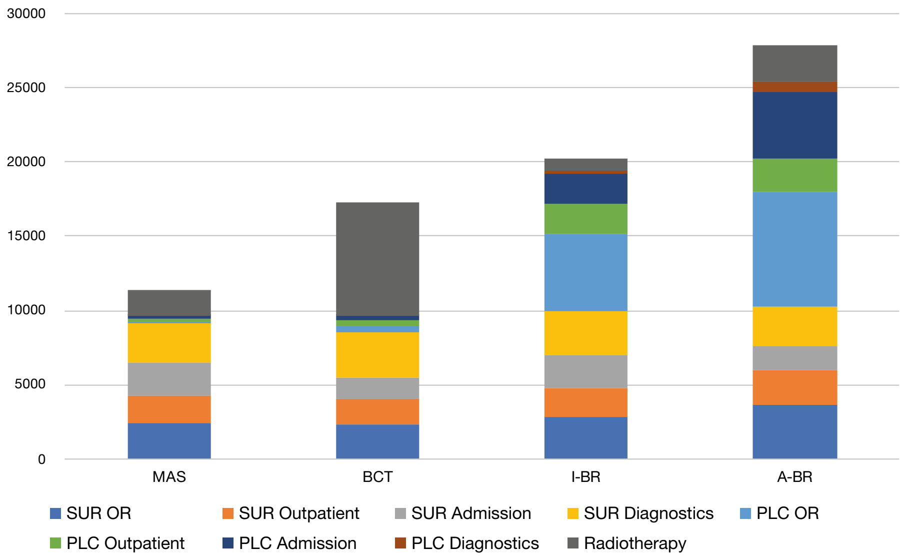
(continued)

Table 2. *Continued*

Full-incremental CE analysis	QALYs	Costs	Incremental QALYs	Incremental Costs	ICER
MAS	7.53	€ 10 933			
I-BR	7.85	€ 19 275			Dominated by BCT
A-BR	7.85	€ 25 846			Dominated by BCT*
BCT	7.87	€ 16 761	0.34	€ 5 828	€ 17 246

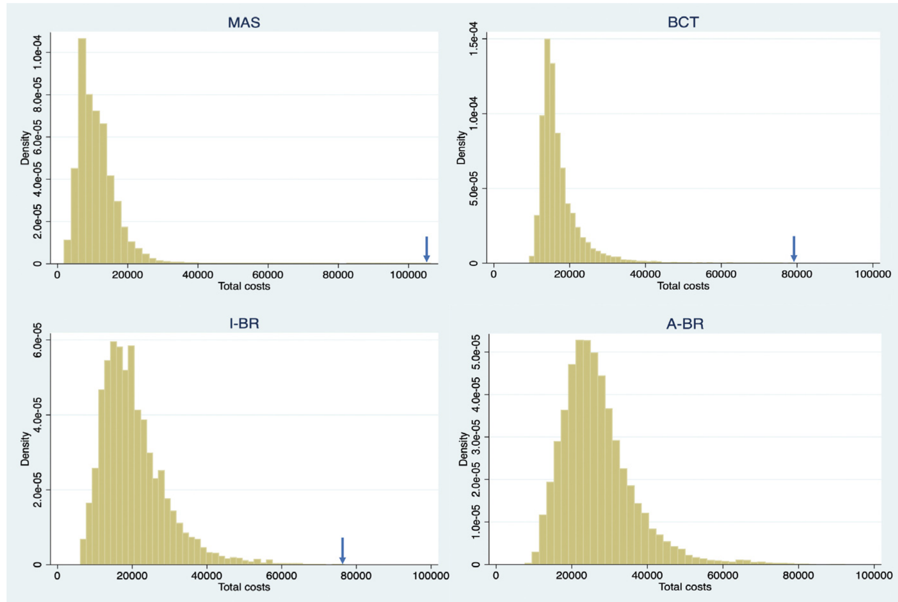
MAS: mastectomy without breast reconstruction, BCT: breast conserving therapy, I-BR: mastectomy with implant breast reconstruction, A-BR: mastectomy with autologous breast reconstruction, QALY: quality adjusted life year. Applied discounting rates: minus 4% per year for costs, minus 1.5% per year for effects. Note that both pairwise and full incremental cost-effectiveness analysis are presented, only the full-incremental analysis takes all the available treatment into account in its assessment. If a treatment is cheaper and more effective it dominates the other treatment (Dom.). The differences between QALY gains can be small, cost-effectiveness ratios can be extremely large, as differences in costs are divided by a very small QALY effect.

Figure 1. Distribution of costs sources per treatment pathway over a 10-year period



Average costs (in euros) per cost-category for each of the four different treatment pathways. MAS: mastectomy without breast reconstruction, BCT: breast conserving therapy, I-BR: mastectomy with implant breast reconstruction, A-BR: mastectomy with autologous breast reconstruction. SUR: surgical oncology, PLC: plastic surgery, OR: operation related costs, Outpatient: outpatient related costs, Admission: admission related costs, Diagnostics: diagnostics related costs.

Figure 2. Histograms of total costs per individual patient for each treatment pathway



Histograms of total costs (in euros) per individual patient for each treatment pathway. MAS: mastectomy without breast reconstruction, BCT: breast conserving therapy, I-BR: mastectomy with implant breast reconstruction, A-BR: mastectomy with autologous breast reconstruction. The arrows signify the patient with the highest costs in the treatment group. Please note that the one outlier in the autologous-BR group with costs of €401 953 is not depicted in the histogram. For this reason, no arrow indicating the patient with the highest costs is depicted for A-BR.

Oncological surgery costs

Over the course of 10 years, BR led to substantially higher mean oncological surgery costs compared to mastectomy and BCT, which can primarily be attributed to operation related costs and outpatient clinic costs. BCT had lower admission and OR costs compared to mastectomy but was associated with higher diagnostics costs.

Plastic surgery costs

The mean total costs for plastic surgery care for autologous-BR were €5,426 (or +57%) higher than for implant-BR over the course of 10 years. Compared to implant-BR, almost all of the additional costs of autologous-BR were associated with admission costs (+€2,445 or, +121% higher), and operation related costs (+€2,408 or, +46% higher).

Radiotherapy costs

As expected, BCT had the highest costs for radiotherapy (€7,606), representing almost half of the total costs associated with the BCT treatment pathway. Conversely, implant-BR had the lowest radiotherapy costs which is probably due to the relative contraindication for implant-BR with radiotherapy.

Quality Adjusted Life Years (QALYs)
No substantial differences existed between the aggregated QALYs of BCT, implant-BR and autologous-BR. However, these three surgical treatments did have a substantial QALY gain over mastectomy of 0.34, 0.32, and 0.31, respectively, over a 10-year period after discounting.

Incremental Cost-effectiveness Ratio (ICER)
Because of the slightly better QALY effects and the substantial lower costs, the full-incremental analysis showed BCT to 'dominate' both implant-BR and autologous-BR and was the most cost-effective treatment. This means that BCT was more effective with less costs. Note when the differences between QALY gains become as small as in this investigation, cost-effectiveness ratios can be extremely large, as differences in costs were divided by a very small QALY effect.

Complication related costs

Table 3 shows an overview of the cost differences between surgical pathways with and without an additional surgical intervention within 60 days. The impact of complications on the costs was substantial, even up to 80% in plastic surgery related costs after autologous-BR.

Table 3. Cost differences between surgical treatment pathways with and without complications

	MAS		BCT		I-BR		A-BR	
Mean costs difference								
Oncologic Surgery	+€4 046	+50%	+€3 637	+48%	+€2 821	+32%	+€1 353	+14%
Operation	+€1 694	+81%	+€1 736	+93%	+€1 280	+56%	+€677	+19%
Outpatient	+€136	+12%	+€198	+18%	+€153	+11%	+€113	+7%
Admission	+€1 531	+86%	+€1 372	+142%	+€946	+57%	+€215	+15%
Diagnostics	+€297	+15%	+€87	+4%	+€271	+12%	+€283	+14%
Plastic Surgery	+€434	+112%	+€1 040	+124%	+€2 996	+36%	+€10 009	+80%
Operation	+€163	+243%	+€547	+181%	+€1 467	+32%	+€4 682	+72%
Outpatient	+€67	+33%	+€163	+60%	+€280	+17%	+€980	+51%
Admission	+€178	+294%	+€293	+167%	+€1 061	+68%	+€3 479	+97%
Diagnostics	+€18	+74%	+€28	+69%	+€74	+46%	+€658	+150%
Radiotherapy	-€1	+0%	+€53	+1%	+€55	+7%	-€516	-20%
Total costs	+€4 478	+44%	+€4 729	+29%	+€5 871	+33%	+€10 846	+44%

Absolute (in euros) and relative (in %) mean cost differences between treatment pathways with and without complications. MAS: mastectomy without breast reconstruction, BCT: breast conserving therapy, I-BR: mastectomy with implant breast reconstruction, A-BR: mastectomy with autologous breast reconstruction. A treatment pathway with postoperative complications was defined as patients who were re-operated within 60 days after the previous operation.

Sensitivity analyses

Raising or lowering the OR costs by 20% did not lead to any substantial changes in the relative cost-effectiveness between treatments. In the second scenario sensitivity analysis, a worst-case scenario assumption was made that all implant-BR patients needed to undergo a re-operation in year 10 for implant replacement and for which all associated additional costs were taken into account. After simulating this worst-case scenario, autologous-BR would still be over €4,500 (+21%) more expensive than implant-BR. The third scenario sensitivity analysis showed that reductions in complication rates may bring the ICER between implant-BR and autologous-BR down quickly from the very high value we found in our study, to more acceptable levels from an estimated €80,000/QALY after a 40% reduction in complication rates to even below €50,000/QALY following a 60% reduction.

Discussion

The present cost-effectiveness analysis of the four most common surgical treatment pathways for breast cancer suggests that BCT is the most cost-effective treatment option if the breast mound is either preserved or reconstructed. Both implant-BR and autologous-BR were considerably more expensive than BCT, with no additional QALY benefits, which made that they did not classify as cost-effective alternatives over BCT.

Longitudinal costs studies which compared autologous-BR and implant-BR have shown mixed results; some found higher costs associated with autologous-BR, while others reported similar or lower costs associated with autologous-BR.[28-35] Pinpointing where these differences arise from is complex due to the aggregated character of the results, differences in methods, reimbursement systems and practices, and last but not least, possible difference in success rates and quality of the local surgical interventions.

In a recent meta-analysis of 16 studies by Khajuria et.al., it was found that autologous-BR is more cost-effective and is associated with better QoL compared to implant-BR.[26] However, the quality of these studies was considered poor and showed high degrees of bias. This might explain why we could not replicate the favorable results of autologous-BR over implant-BR. Other reasons for this discrepancy may be that previous cost-effectiveness studies used QALY estimates that were either gathered from a panel of experts, who imposed a large QALY difference in favor of autologous-BR, or that in some studies QALY scores based on converted scores from the condition-specific Breast-Q were used.[20, 30, 32, 36, 37,45] Outcomes that are derived from the condition-specific Breast-Q questionnaire inherently suffer from a focus-effect.[38] This is because the BREAST-Q questionnaire focusses on QoL related to breast surgery and differences in treatments are measured on that subset of QoL instead of complete health-related QoL profiles which a QALY should represent.[20] Moreover, the values used may not necessarily reflect societal preferences for health outcomes. As Matros et al. considered their outcome

"Breast QALYs" they implicitly recognized that their values do not represent generic QALYs as prescribed by the guidelines of cost-effectiveness research. By using expert opinions and condition specific measures instead of using validated generic utility measures based on societal preferences, previous studies may have magnified the differences in QoL outcomes between the different surgical treatments, making these so-called "QALY" outcomes unsuitable for comparison with other medical interventions. This overvaluation of effects may have allowed to off-set the high costs, which are associated with autologous-BR procedures. However, after using an appropriate generic QALY measure as the EQ-5D, the large beneficial effect of autologous-BR seems to disappear.[11, 39]

Many studies on BR outcomes suffer from risk of bias, design problems and substantial discrepancies in reported complications.[26, 40] The lack of reliable, comparable and comprehensive data on complications and resource use in treatment pathways for BR, BCT and mastectomy motivated us to perform a large empirical cost-utility analysis (i.e. that is a cost per QALY analysis) using real patient data instead of performing a simulated decision-making model such as a Markov-model. A consequence of this choice was a more limited time-horizon for the analysis.

For autologous-BR to become cost-effective compared to implant-BR, its QALY gain needs to improve. One reason we believe the QALY gain of autologous-BR in real-life lags behind the expected value by physicians, is that complications of autologous-BR procedures, which occur relatively frequently, have a large and long-lasting negative impact on the QoL of patients.[11, 40] Autologous-BR complications are at the same time associated with very high additional absolute and relative costs, with a €10,009 (80%) increase in plastic surgery costs compared to an uneventful course. This suggests that a potentially effective way to improve the cost-effectiveness of autologous-BR techniques would be a reduction of the incidence of complications. The scenario sensitivity analysis showed that reductions in complication rates can quickly bring the ICER of autologous-BR down from the very high value we found in the present study to more acceptable levels, ranging from an estimated €80,000/QALY after a 40% reduction in complication rates to even below €50,000/QALY following a 60% reduction. This scenario analysis showed that large reductions in complication rates of autologous-BR can potentially allow autologous-BR to attain acceptable cost-effectiveness levels compared to its most important alternative, implant-BR. Further studies on patient selection and risk factor reduction will be required to study the possibilities to reach such reductions in complication rates following autologous-BR.

Limitations

The current study was not a randomized controlled trial (RCT) but an observational study, which included all patients who had been treated during the study period and who fulfilled the inclusion criteria. This means there were differences in pre-treatment characteristics between the patients. The effects of pre-treatment differences were in part reduced, as we used adjusted quality of life weights (utilities) to estimate the QALY outcomes. These quality of life weights came from a previous study that used propensity score matching to adjust for pre-treatment differences between the treatment groups. But obviously quality of life was not the only factor which may have been influenced by the pre-treatment differences. The health resource use/costs aspect of the CEA may also have been influenced by factors such as age of the patient, tumor stage, existing comorbidities and other factors. Although we would have wanted to correct for such factors, the current methodology unfortunately did not allow us to do so. This means that the results should be interpreted with caution. However, we presume that the imbalance between the groups may have mainly led to relatively older and more fragile patients with more comorbidities in the mastectomy and BCT groups, which may have lowered the aggregated QALYs and raised the costs of these two treatment groups. This means that if we would have had the opportunity to correct factors such as age and comorbidity, this would likely have further decreased the cost-effectiveness of implant-BR and autologous-BR compared to BCT and mastectomy.

The current study only included costs from the intramural healthcare provider perspective instead of also including societal costs that the patient and its surroundings may have incurred as a consequence of the disease and its treatment (e.g., productivity loss, transportation, visits to the GP, physiotherapist, psychologist, and also second opinions at other hospitals or visits to emergency rooms outside of the studied hospitals). All these aspects together may have led to an underestimation of the total incurred costs related to the different treatment pathways. Further research should investigate whether including the additional costs from the societal perspective would change the relative cost-effectiveness outcomes.

The results of the current study are based on the Dutch healthcare system and may not be directly extrapolated to healthcare systems of other countries. However, we believe that although the absolute costs may not be identical, the results of this study do provide a good insight in the relative costs of the different treatment pathways.

Clinical implications

Although this was a cost-effectiveness study, the results have implications for clinical decision-making. First of all, it seems that compared to mastectomy, BCT and BR produce more QALYs. Consequently, if mastectomy is not the only option, patients should be informed that BCT and BR on average provide more benefits. When considering autologous-BR, patients should be informed that if a postoperative complication occurs, for which the risk is relatively high,[34] it has long-lasting negative effects on QoL and requires a substantial amount of additional medical care. If the patient is risk averse in considering the trade-off between the expected outcomes and the risk of complications, autologous-BR would not be the preferred option. Finally, if BCT is feasible, it is a good starting point of any clinical deliberation between surgical options, as its oncological outcomes are comparable to mastectomy,[41] its QoL outcomes are comparable to BR and surgery is more straightforward with the least complications.

Conclusions

The results of the present study suggest that mastectomy provides the least benefits for patients. When the other surgical treatment options are considered, the full-incremental cost-effectiveness analysis showed BCT was less expensive and showed a marginally more favorable QoL, thereby dominating over both implant-BR and autologous-BR. BCT had an ICER of €17,246/QALY compared to mastectomy. QoL and costs of autologous-BR seem to be strongly affected by the relatively high occurrence of complications, which prevented autologous-BR from reaching acceptable cost-effectiveness levels compared to implant-BR. If reconstruction of the breast mound following mastectomy is considered, implant-BR seems to be the most cost-effective technique. As far as cost-effectiveness is concerned, BCT seems the best surgical treatment of choice for breast cancer patients.

Acknowledgements

We would like to thank all hospital administration personnel who have helped collecting the research data for their time and effort. Kelly M. de Ligt for her assistance with parts of the text. We are indebted to the Esser Foundation for financial support and more specifically to Prof.dr. S.E.R. Hovius for initiating and facilitating this cost-effectiveness study.

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Chapter 5

Patients' and surgeons' experiences after failed breast reconstruction: a qualitative study

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Journal of Plastic, Reconstructive & Aesthetic Surgery.

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Abstract

Background
The goal of postmastectomy breast reconstruction (BR) is to improve the quality of life of patients. However, complications following autologous (A-BR) and implant-based breast reconstruction (I-BR) occur frequently and may even lead to BR-failure, which can be a distressing event for both patients and surgeons. The current study therefore looks at the experiences of both patients and surgeons after a BR-failure.

Methods
Patients with a failed BR from a large multicenter cohort study and participating plastic surgeons were invited to participate in semi-structured interviews focusing on their experiences. The interviews were analyzed according to the principles of grounded theory.

Results
Fourteen patients with a failed I-BR, four patients with a failed A-BR and four plastic surgeons participated. Three main categories emerged from the data: personal experiences with BR-failure, the motives for a redo of a failed BR, and patient-surgeon communication. Patients would like to be treated with more attention to their personal feelings and lives, instead of being approached from a purely medical-technical perspective. Surgeons may experience feelings of guilt leading to the strong urge to fix the failed BR, whereas patients may be less inclined to undergo additional operations. Patients want to know what the choice for a particular type of BR would mean to their personal lives. The impact of I-BR-failure may be underestimated and requires the same degree of intensive aftercare and attention.

Conclusions
Implementing the recommendations of this study in clinical practice may facilitate improvements in how both patients and surgeons cope with a BR-failure.

Introduction

A significant proportion of breast cancer patients either require or actively opt for a mastectomy. Breast reconstruction (BR) aims to reduce the negative effects the loss of one or both breasts may have on psychosocial health, body image, and sexual function.[1] However, BR also has relatively high risks of complications, and can sometimes even result in the complete loss of the reconstructed breast (BR-failure). A recent large-scale prospective study reported BR-failure rates of 7.1% for implant-BR (I-BR) and 1.3-2.1% for autologous-BR (A-BR).[2]

Few studies have investigated the potential negative psychological consequences of a BR-failure. One recent qualitative study showed that an A-BR failure has a large emotional impact on patients.[3] Quantitative studies by our research group have shown that postoperative complications (including BR-failures) were associated with substantial psychological distress in the short-term, but that in the long-term, these levels of distress returned to values comparable to that of patients without such postoperative complications.[4,5] However, quantitative studies do not provide insight into which experiences lead to distress in patients confronted with a BR-failure. Qualitative studies which investigate the effect of an implant-based BR-failure on patients' quality of life are lacking.

In addition, plastic surgeons who perform the procedure may also be profoundly affected by the event of a BR-failure. Several studies have shown that the occurrence of serious adverse events may have a strong impact upon the healthcare provider involved, also referred to as the "second victim" phenomenon.[6,7]

The aim of this study was to explore both patient and surgeon views and experiences of A-BR or I-BR failure, in order to obtain insights that could facilitate improvement in care for both parties.

Methods

Study Design

We performed face-to-face, semi-structured, in-depth interviews with patients following a failed BR and with plastic surgeons involved in BR-surgery (J.G. and M.H.). Interview data was analyzed according to the principles of grounded theory. This method was chosen because of its ability to develop an explanatory theory that is grounded in and systematically derived from data with minimal interference of preconceived ideas of the researchers or existing theories[8-10]. It involves a cyclical process of collecting data, analyzing it, developing a provisional coding scheme, using it to suggest further sampling and analysis, verifying emerging theory and so on. A model was constructed through analysis of the data by two independent researchers (C.K. and L.H.). BR-failure was taken as one group and in principle no distinction was made between A-BR and I-BR. This study was approved by the Medical Ethics Committee of Leiden University Medical Centre (NL18441.058.07).

Study Samply

Patients
Patients with a failed BR who had participated in a prospective multicenter follow-up study on postmastectomy BR for breast cancer or prophylaxis were invited to participate in this study to obtain a representative sample.[4,5,9,10] Due to the limited number of patients with an A-BR failure in the study, additional patients from one of the participating hospitals were recruited. All patients signed an informed consent.

Surgeons
Plastic surgeons involved in BR were invited to participate in this study. The plastic surgeons provided oral informed consent.

Data Collection

A topic-based interview guide was used to conduct the interviews in a semi-structured manner. For patients it focused on: medical history, communication with their plastic surgeon during the BR trajectory, the motivation for a potential redo of the failed BR and impact of the failed BR. For plastic surgeons: first reactions to a failed BR, ideas on consequences of a failed BR for the patient, ideas on aftercare for patients and (emotional) impact of the BR-failure on him/herself. Participants were encouraged to elaborate on the different topics. Additional questions were asked to acquire specific details beneficial to the study. All interviews were audio-recorded and transcribed verbatim.

Data Analysis

Data was imported and analyzed using NVivo software.[11] Next, two members of the research team (C.K and L.H.) independently performed open coding in which the researchers independently went through the transcripts line by line and assigned labels to text elements, which were then grouped into key concepts. This process was continued until the two researchers separately worked through the entire set of interviews where the coding framework continually developed and was adjusted based on the data. After this phase the two researchers together compared and integrated their coding frameworks and clustered the derived concepts into themes. Subsequently, the research team (C.K., L.H., L.K. and S.I.) met to discuss initial findings followed by comprehensive review and adjustment. Themes were grouped into categories and a final theoretical framework was agreed upon. The accompanying codebook was used for the complete dataset. The results of this final analysis are presented in the results section.

Results

Eighteen patients (out of 39 BR failure patients) were included, of which four patients had undergone A-BR and 14 I-BR. Thirteen patients declined to participate, one was not approached as she was undergoing treatment for metastatic breast cancer, one was not approached because of complex psychopathology, and six were not approached because of saturation of the specific study group. Four plastic surgeons were included. At the time of interview, patients were on average 52 years old (SD 11.5) and their age varied between 30 and 66 years. Two male and two female plastic surgeons participated of whom three had extensive experience with both I-BR and A-BR. One surgeon was mainly experienced in performing I-BR. Their experience as a certified plastic surgeon ranged between 8 and 15 years. One third of the patients had undergone a prophylactic mastectomy. The interviews with both patients and surgeons lasted about one hour on average. Three main categories emerged from analysis of the data: 1. personal experiences with BR-failure; 2. motives for a redo of the failed BR; and 3. patient-surgeon communication.

1. Personal experiences with BR-failure

1.1 Experiences of the patient

1.1.1. The patients' personal experience of their BR-failure
The patients' experience of their BR-failure could be divided in two subthemes: physical impact and psychosocial impact. Patients experienced several, sometimes persisting, physical symptoms after BR-failure, including pain, weight loss and fatigue. Cognitive problems were also described, such as memory loss and concentration problems, which they ascribed to repeated general anesthesia in a short period.

Besides the physical impact, BR-failure also had a high psychosocial impact. In our sample, BR-failure often led to body dissatisfaction. Women stated that their bodies looked horrible after the failure and one participant even described the feeling of being mutilated *("I hated my body so much. It was a battlefield. Yes, it is… it is just disgusting. Just sickening. That is what it looked like." – 2045)*. Almost each participant described that they felt less feminine, which negatively affected their self-esteem. They described that they felt ashamed of their bodies after the BR-failure. One woman, who had been able to overcome her shame after an extended period of time, perceived this as a great victory *("I let a few tears of joy when I was wearing my bikini again. I thought: I have come this far… this is the reason why I have done this. And then I thought: this is a big victory for myself." – 4079)*.

Patients had experienced a broad variety of emotions during the failed BR course, including feelings of fear, anger, disappointment and relief. Most patients preferred to use their own social system to support them in coping with these feelings over seeking professional help, even if it had been offered to them. Some women described negative consequences for their sexual relationship. They described issues with intimacy due to shame and less spontaneity in initiating sexual activities ("You are ashamed to death when you're naked in the bathroom or in bed. Lights off, bye, I'll hide myself. I always wear a shirt now, while I used to wear nothing when sleeping. Yes, you just feel very ugly" – 2045). Some women mentioned they find it a difficult topic to discuss with their partner. A few even feared that their relationship would collapse *("I am worried, because if a man misses passion… what if he meets someone else who can fulfill those needs? Yes… I do not want to think about that." – 2089)*.

1.1.2 The patients' perceptions of their plastic surgeon's experience of the BR-failure
Some patients thought that their plastic surgeon felt sorry for them, because he or she was very committed to the patient during the entire course *("He was literally crying while he was cycling from one hospital to another, because he wants to be there, because he wants to help you. He had been rinsing those implants for like half an hour. That is incredible." – 2006)*. Other patients thought that their plastic surgeon did not necessarily feel bad for them, rather he/she found it especially difficult for himself/herself. Those women were able to empathize with their surgeon's frustrations and possible feelings of guilt and failure.

1.2 Experiences of the plastic surgeon

1.2.1 The plastic surgeons' experience of the BR-failure
Factors of influence on how surgeons experienced a BR-failure included *"the chemistry"* with the patient, type of reconstruction (A-BR vs I-BR) and the cause of the BR-failure. Regarding the type of reconstruction, the surgeons described a greater impact if it had been an A-BR-failure *("The loss of a tissue expander or breast implant, that is of course annoying. Everyone is frustrated with such a loss. But I am really upset with the loss of a DIEP flap. I really do not like that" – PCH1)*. The plastic surgeons questioned the possible causes of the failure. One surgeon stated it would be easier to accept a failure if his performance would not be the cause of it, whereas another plastic surgeon indicated their preference to make a clear mistake, instead of not knowing the cause at all. Although a BR-failure does not occur often, the plastic surgeons reported that it has had a big impact on their self-confidence. One plastic surgeon even considered to stop performing breast reconstructions. Plastic surgeons also reported they had become very cautious in their patient selection, implementing more (unnecessary) backups in the procedure. They stated it had taken them a few successful A-BRs before they had been able to return to normal practice again. They report that they now more clearly point out the possibility of a BR-failure while informing the patient.

1.2.2 The plastic surgeons' perceptions of the patient's experience of the BR-failure
All plastic surgeons acknowledged that a BR-failure has negative consequences for patients' emotional wellbeing, body-image, relationship and sexuality, however they did not elaborate much further on it.

2. Motives for a redo of a failed breast reconstruction

2.1 Patients' motives to undergo or not undergo a second BR

2.1.1. Motives in favor of a second BR
The most common reason for undergoing a second BR was body dissatisfaction. One woman stated that the daily confrontation with her deformed body made her feel so miserable, that she had no other choice than to undergo another reconstruction. Another woman reported she had been persuaded by her surgical oncologist *("I was done with it; I had closed this topic… The next year, he mentioned it again. He said: 'You have to do something about it, it can be much better.'" - 2069)*. Other reasons mentioned include young age, confidence in a positive outcome and frustration related to using an external prosthesis.

2.1.2 Motives against a second BR
The most mentioned motives for not undergoing a second BR were the risks and fear of complications, fear of putting health at risk, and the burden of the surgery and its recovery *("…but I don't want it anymore. I've been poked and picked at enough, it's done, I leave it like this... I'm tired of surgery and pain." - 4083)*. The impact of undergoing general anesthesia was mentioned frequently as a part of the surgery's burden. Other reasons included the feeling that it was unnecessary at their older age, acceptance of the current situation, and uncertainty regarding the outcome.

2.2 The plastic surgeons' view regarding a second BR attempt

Compared to the patients, responses from the surgeons were less balanced. One plastic surgeon stated that in his/her practice every woman with a failed autologous reconstruction undergoes a second BR, and two reported that the vast majority of their patients choose another reconstruction. The plastic surgeons agreed that patients need time to recover mentally as well as physically from the BR-failure before undergoing the next surgery *("Sometimes I suggest you first have to feel comfortable again before you can take the next step." - PCH 3)*.

3. Patient-surgeon communication

3.1 Patients' experiences with communication with the surgeon

3.1.1. Contact with the surgeon

Both positive and negative experiences in relation to contact with the surgeon were reported. Some women noted that a good relationship with their plastic surgeon increased their confidence in a positive outcome. Other women decided to go to another plastic surgeon as a result of the contact they had with their plastic surgeon. Arrogance was mentioned a number of times as an irritating quality *("If they were only just a little bit human and not that proud-hearted... Those plastic surgeons are that terribly arrogant, you cannot really say to them that something went wrong." – 2045)*.

3.1.2 Patients' experience with receiving information

Patients stressed the need to receive adequate information about: the various treatment options; the psychosocial impact of a BR in general and the possible outcomes when things do not go according to plan, for instance in case of failure. The need for adequate preoperative information regarding the psychosocial impact was mentioned most often. Patients missed information about, for example, body-image, the possible impact on their relationships and intimacy, and the postoperative care. Furthermore, women wished to have received a clearer picture of what the different outcomes would have meant for them in their daily lives.

3.1.3 Communication about the BR-failure

An overarching theme that emerged from the discussions on communication about the BR-failure was the desire by patients to be seen and treated as individual human beings, with regard being given to their personal feelings and lives. All women underscored the importance of empathy and they expressed a desire for explicit recognition of the emotional impact of the BR-failure by their plastic surgeon. The patients considered it important that the plastic surgeon be accessible, honest and dedicated and that they create time to discuss their personal needs and issues in a compassionate manner.

3.2 Plastic surgeons' views on communicating with the patient

3.2.1 Information provision and counselling

All plastic surgeons acknowledged the importance of providing adequate information. They all stated they discuss the patients' expectations very extensively. Most plastic surgeons reported they only provide general information about possible complications to the patient. Furthermore, surgeons paid limited attention to the psychosocial impact of the failure *("I am not going to talk about sexuality explicitly, I think that's not necessary. It is clear that she has a problem with her own body. I will not discuss that into depth." – PCH 2)*.

3.2.2 Communication with the patient after a BR-failure

Some surgeons emphasized the importance of clear and honest communication about the cause of the failure and follow-up steps. They pointed out the importance of their own involvement in the situation and social support for the patient was widely acknowledged by the plastic surgeons. However, the usefulness of professional psychological support was questioned by the plastic surgeons. *("I think it is very important for the surgeon to keep in direct contact with the patient and not someone else ... I think that doesn't help, not very much though. Maybe if the patient gets a psychological reaction, such as a reactive depression or something. But I have never seen that before. But I do know that the patient is very much in need of contact with the surgeon." - PCH 2)*.

Discussion

A finding that may have important clinical implications and that would be easy to implement relates to the strong focus of plastic surgeons on A-BR failure. Although the surgeons were interviewed about the impact of BR-failure regardless of type of reconstruction, they almost exclusively talked about the impact A-BR had had on them with limited discussion about the impacts of I-BR. One surgeon even explicitly acknowledged they are only intensively involved in the aftercare when there is an A-BR failure. This suggests that the impacts of I-BR are underestimated. This is in contrast to how a patient experiences the failure, because nothing in our study has suggested that I-BR patients experienced their BR-failure as less distressing than A-BR patients. One might even suggest some I-BR patients were more taken aback by their failed BR, as they seemed less prepared and informed about this possible complication than A-BR patients. Although an I-BR-failure may have a less severe impact on the plastic surgeon, this is not necessarily the case for the patient. Therefore, the same high degree of involvement in the aftercare for the patient and attention for the psychosocial impact is required for I-BR patients, specifically when taking the considerably higher rate of I-BR failures into account.

One of the most frequently returning themes among patients was their desire to be seen and treated as an individual human being, with attention being given to their personal feelings and life, instead of being approached from a purely medical-technical perspective, in line with earlier research.[3] More concretely, patients expressed the desire their plastic surgeon would ask them how they were doing and explicitly acknowledged the emotional impact of the BR-failure.

Even a simple question that confirms the surgeon's empathy like "How are you doing?" or the acknowledgement "It's really tough, isn't it?" would make a difference for the patients. So, why do doctors not address the psychosocial aspects/impact of the BR-failure? A possible explanation lies in the fact that the occurrence of a serious adverse event (i.e., a complication) may also have quite an emotional impact on the surgeon involved.[6,7,12] This impact seems greatest in the period directly after the incident, and this is exactly the period when the patient's need for a conversation about the failure is the highest. We found that surgeons' feelings of failure, self-doubt and guilt were present during this phase. Dealing with the emotions of the patients and their family has been reported to be particularly difficult when physicians are dealing with unresolved emotional reactions themselves.[6,7,12] In our study, one plastic surgeon reported that seeing the patient with a failed BR was a constant reminder of the time he/she had failed. Addressing the emotional impact of the BR-failure for the patient would make the suffering of patients very tangible, and, in that way, confronting.

Another returning theme in the interviews was the desire of the patients to understand what the choice for a particular type of BR would mean for them as a person. They stated that almost all the information they had received, had been focused (too) exclusively on medical-technical information and the aesthetic results. This is in line with the findings of previous studies regarding information provision about BR.[3,13,14] Patients in our study specifically stated they would have liked to be informed on the psychosocial impact of a BR and/or BR-failure. Paying attention to these aspects may also benefit the entire consultation, as patients experience the conversation as more personal. Acknowledging beforehand that the BR procedures may have a substantial psychosocial impact may also help patients deal with these issues more effectively in case they occur.[15]

A final important result of our study is the discrepancy between the views of patients and plastic surgeons regarding the necessity to perform repeat surgery after the BR-failure. Some surgeons seemed to assume that almost all patients want a redo of their BR. However, this was not what we found in the patient group. A large proportion of patients reported they did not necessarily want a redo of the BR and listed numerous reasons for this. After the BR-failure, patients have gained firsthand experience on what it means to undergo a BR followed by a severe complication, something which almost all stated they did not have a clear idea about beforehand. A previous study showed that complication risk is a major factor in influencing patient decision making regarding future BR procedures.[16] Surgeons may experience feelings of guilt that they have not been able to give the patient what they came for and experience a strong urge to fix this. It is therefore important to thoroughly review the patient's motives before making a well-informed, shared and considered decision on whether or not to undergo a repeat BR.

Strengths and limitations of the study

The current study is a retrospective, qualitative analysis of the experiences of both patients and plastic surgeons with the occurrence of BR-failure. The retrospective nature of this study holds the risk of recall-bias. Memories of the events related to the BR-failure may have been colored by the outcome, current feelings about BR and the BR course. A strength of this study is that all interviews were independently analyzed by both a psychologist (L.H.) and a medical doctor (C.K.) to minimize bias that could originate from either respective professional perspective. The current study was not designed to compare differences in the impact of BR-failure between A-BR and I-BR and as such does not report explicitly on this in the results. Moreover, there is a preponderance of I-BR patients included in this study, despite our efforts to include more A-BR patients. This imbalance may have influenced our findings. Further research is needed to evaluate similarities and differences between the two treatment modalities.

Conclusions

The impact I-BR failure has on the patient should not be underestimated or considered negligible compared to A-BR failure, and patients require the same high degree of attention and aftercare, specifically when taking the considerably higher rate of I-BR failures into account. For all patients with a failed-BR, explicit acknowledgement of their suffering and emotional well-being by their plastic surgeon is an important part of their recovery. Empathy and good clinical conversation skills of the surgeon may be more beneficial than immediately offering additional psychosocial interventions. However, plastic surgeons may have difficulty with this, as they are still struggling with their own emotional response to the BR-failure. Interventions could focus on a safe and supportive debriefing environment for the surgeons to discuss the BR-failure with colleagues. Such interventions could ultimately improve the well-being for both the patient and surgeon.

Acknowledgements

The authors thank all women and plastic surgeons who participated in this study. We would like to thank Mirjam Hoefkens (M.H.) who played an essential part in the initiation of the study and conducting the interviews.

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Chapter 6

Why we should counsel breast cancer patients more towards breast conserving therapy

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After the diagnosis breast cancer is made, the first choice a patient with breast cancer and her surgeon together need to make is between breast conserving surgery followed by radiation therapy (breast conserving therapy, BCT) or mastectomy, which may be followed by breast reconstruction (BR). In discussing the pros and cons of these options, quality of life considerations will be the main topic, as there are no differences in survival rates.[1] In a large multicenter cohort study, which compared quality of life (QoL) between breast cancer patients following BCT, mastectomy only, and mastectomy followed by implant- or autologous-BR, we showed the added value of breast preservation and reconstruction over mastectomy only.[2] However, no clinically relevant differences in overall health-related QoL were found between BCT, implant-BR, and autologous-BR. This was remarkable, as other studies have shown differences in QoL outcomes. This may partly be explained by differences in QoL questionnaires used. Mostly, disease-specific QoL instruments have been used, with separate scales that each focus on different aspects of breast surgery, such as breast appearance and chest symptoms. However, this may have the undesirable consequence that overall health effects of the various surgical treatment pathways are missed, like the negative effects of complications on health-related QoL, if they are not directly breast-related. Therefore, we used a generic QoL instrument, the preference-based EQ-5D, and we found that postoperative complications had a large and long-lasting negative impact on QoL of patients, specifically following autologous-BR.[2]

There are also societal arguments to consider. Because we used the EQ-5D and because we were able to estimate the costs associated with the various surgical treatment pathways, we were able to estimate the cost-effectiveness in terms of costs per Quality Adjusted Life Year (QALY).[3] Using our large data set, we found that BCT had the most favorable cost-effectiveness ratio compared to the other options. Our results deviate from earlier cost-effectiveness studies about breast reconstruction or conservation. We argue that this is because most other cost-effectiveness studies used 'expert' opinions to estimate the value of the different breast reconstruction outcomes. If experts are enthusiastic about the improved breast appearance and do not think that the potential complications produce much disutility, then the results are pushed towards a favorable outcome for autologous-BR with a high risk of complications and little additional QoL benefits compared to implant-BR or BCT. In other words, as long as experts instead of patients value the outcomes of benefits and risks, the outcomes of the related studies become dependent on the perception of these experts. As we used values derived from patients themselves, we could value the outcomes of BR more objectively, independent of our own professional beliefs and hopes. Using these patient-derived QoL values, BCT had the most favorable cost-effectiveness compared to the other options.[3]

Do the favorable outcomes of BCT both in terms of QoL and cost-effectiveness mean that clinicians should always counsel patients towards BCT? We think that such a mechanistic implementation would miss the point of the results presented. Our results suggest that 'on average' BCT is a good starting point for a consultation about possible treatment options. If patients have a clear preference for the expected outcomes of the reconstruction options and/or are reluctant towards the effects of radiation therapy, and

are willing to trade-off the risk of complications, then breast reconstruction could be considered. From a health policy point of view, cost considerations might provide an additional argument. Health policy should look beyond the patient in question, and also consider the lost opportunities of other patients if money is spent on the patient in question. However, we do not suggest that health policy should always favor BCT, given its favorable cost-effectiveness. Again, the cost-effectiveness ratios are based on average patients, and cost-effectiveness will most likely improve if treatments are allocated rationally and in line with the preferences of a well-informed patient.

What complicates the situation, are studies that showed a larger risk of the development of a rare and potentially lethal anaplastic large cell lymphoma (BIA-ALCL) after implant-BR than was previously assumed.[4] This news has been widely picked-up by the media and has led to a ban on certain breast implant types in some countries over the world. It has also led to fear and many questions among patients who previously have undergone implant-BR, and among patients who are about to make a choice with respect to whether and which type of BR they would opt for. These findings strengthen the case for BCT. However, please note breast conserving surgery must always be followed by radiotherapy and thereby is inevitably associated with adverse effects. As breast cancer survivors grow in number with increasing life expectancy, research on these adverse radiation effects becomes increasingly relevant to find strategies to reduce them and to improve our knowledge for patient counseling. Overall, these findings ask for a careful discussion of risks and benefits, taking into account the value an individual patient puts to these aspects.

In conclusion, BCT is generally associated with fewer complications, similar QoL, and lower resource use, leading to superior cost-effectiveness compared to mastectomy followed by BR.[3] We therefore believe that patients with breast cancer, for whom BCT is an oncologically safe alternative, should be counseled more towards this treatment. Large differences still exist between countries in the rates at which BCT and mastectomy are performed. For example, in Denmark the mean BCT rate is around 68% compared to around 59% in the Netherlands.[5] This suggests there is room for changes in treatment choices and counseling. An important challenge is educating breast cancer patients about the differences between treatments, with respect to survival, expected QoL, cosmetic outcomes, visits to the hospital and short- and long-term adverse effects of adjuvant treatments. No one-size-fits-all solution exists for this group of patients. Therefore, careful and preferably standardized exploration of the value the patient attributes to all aspects of her future treatment, its process and outcomes is warranted.

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Chapter 7

Discussion

Why we should counsel breast cancer patients more towards breast conserving therapy

In healthcare interventions should prolong life and/or increase quality of life (QoL). These two aspects, a longer life and a better quality of life, are combined in the outcome measure Quality Adjusted Life Years (QALYs). Patients who have been diagnosed with breast cancer will generally focus on the first goal. They want to survive the cancer. After diagnosis, the first choice a patient with breast cancer and her surgeon together need to make is between breast conserving surgery followed by radiation therapy (breast conserving therapy, BCT) or mastectomy. If they opt for mastectomy, the patient will be presented with another choice, whether and how she wants her breast to be reconstructed. In the present thesis it was investigated what it means for the patient and society when a choice is made for one of these different treatment pathways.

Quality of life after breast cancer surgery

Previous studies have understandably focused on what consequences a choice for one of these surgical treatments has on the life expectancy of the patient. Multiple, high quality, large studies have found that BCT has favorable or at least equal survival rates compared to mastectomy in patients with early stage breast cancer.[1-3] Because survival outcomes following mastectomy and BCT are equal and at the same time relatively good,[1] quality of life (QoL) after breast cancer treatment becomes increasingly important. A multitude of measures have been developed to reliably quantify the QoL of breast cancer patients, each with its advantages and disadvantages. However, numerous health care reimbursement agencies such as NICE and ZiNL have propagated that if QoL is used to compare the value of different treatments, the measures used should allow for calculating QALYs. Various agencies prescribe the EQ-5D, which is a generic preference-based health-related QoL measure consisting of 5 items, covering problems with mobility, self-care, daily activities, pain/discomfort and anxiety/depression. Our study (**chapter 2**) showed that such a seemingly simple outcome measure can reliably and validly measure QoL outcomes of breast cancer surgery as well as breast reconstruction (BR).[4] In a large multicenter cohort study (**chapter 3**), which compared QoL (assessed using the EQ-5D-5L, the recommended questionnaire for QALY calculations) between breast cancer patients following BCT, mastectomy only, and mastectomy followed by implant or autologous breast reconstruction (BR), we showed the added value of breast preservation and reconstruction over mastectomy only.[5] However, no statistically significant differences in QoL were found between BCT, implant-BR, and autologous-BR in overall health-related QoL. Postoperative complications had a large and long-lasting negative impact on QoL of patients, specifically following autologous-BR.

Cost-effectiveness of surgical pathways for breast cancer treatment

Healthcare budgets are under substantial strain due to increasing healthcare costs. Society, policy makers and insurance companies are therefore confronted with complex choices about which medical interventions need to be reimbursed. Cost-effectiveness of the interventions is an important argument. This is not only relevant when choosing between surgical pathways for breast cancer treatment, but also when the reimbursement of these surgical pathways is in competition with other allocations of the healthcare budget. This is particularly relevant for common surgical treatment pathways for breast cancer such as BR, as these are not life-prolonging. For this reason, we performed a formal state-of-the-art cost-effectiveness analysis (**chapter 4**). This non-randomized, multicenter cohort cost-effectiveness analysis showed that BCT was the most cost-effective alternative that preserves or reconstructs the breast mound.[6] Both implant-BR and autologous-BR were considerably more expensive than BCT, with hardly any additional benefits (QALYs), which made that they did not classify as cost-effective alternatives over BCT. If reconstruction of the breast mound following mastectomy is considered, implant-BR seems to be the most cost-effective technique. One of the reasons for the more favorable cost-effectiveness of implant-BR over autologous-BR was that the relatively high occurrence of complications had a disproportionately large impact on the outcomes in terms of QoL and costs of autologous-BR, even if reoperations due to long-term implant complications such as implant rupture or capsular contracture were taken into account. The higher costs associated with BR are not only relevant from a monetary perspective; they are a direct result of longer operative times and more hospital admissions and personnel use, which are in their own right scarce resources that should be distributed responsibly.

A noteworthy development in the field of breast conserving surgery is the advent and development of oncoplastic surgery. In oncoplastic surgery, surgical oncologists and plastic surgeons join forces to extend the indication for breast conserving surgery to even larger tumor sizes and previously adverse tumor locations which would have otherwise led to unfavorable/unacceptable cosmetic outcomes.[7, 8] Further studies will need to be conducted on the QoL outcomes and cost-effectiveness of this new promising treatment modality.

Counselling breast cancer patients

Counselling breast cancer patients who need to undergo a mastectomy is complicated. Important to realize here is that BR is considered elective surgery which is aimed to restore the shape of the breast mound; a procedure that does not improve survival and one could even consider a cosmetic intervention. The surgeon and patient need to take this into account when they consider the drawbacks and risks that are associated with the different BR options. Both implant-BR and autologous-BR are associated with relatively high complication risks. A recent large prospective study by Bennet et al. found complication rates of around 26% for implant-BR (with 15% needing a reoperation) and around 47% for autologous-BR techniques (with 29% needing a reoperation).[9] These are high risks for elective procedures. Our study (**chapter 3**) showed that specifically for autologous-BR such complications are associated with a large and long-lasting negative impact on QoL.[5] In addition, our qualitative study (**chapter 5**) showed that if a complication leads to a total BR failure, it is associated with a large impact on both the patient and the surgeon.[10]

Important aspects that came forward (**chapter 5**) and should be considered when counseling (BR-failure) patients are that patients would like to be treated with more attention to their personal feelings and lives and what a choice for one of the treatments would mean for their personal lives, instead of being approached from a purely medical-technical perspective.

There were also differences in expectations following a BR-failure, where surgeons may experience feelings of guilt leading to the strong urge to fix the failed BR, whereas patients may be less inclined to undergo additional operations after learning what it means when an operation does not go according to plan. Furthermore, the impact of implant-BR-failure on patients may be underestimated by surgeons and requires the same degree of intensive aftercare and attention as do patients who have experienced an autologous-BR failure.

To further complicate the situation, an increasing number of reports have shown a considerably larger risk of the development of a rare and potentially lethal anaplastic large cell lymphoma (BIA-ALCL) after implant-BR than was previously assumed.[11] This news has been widely picked-up by the media and has led to a ban for certain breast implant types in some countries. It has also led to fear and many questions among patients who previously have undergone implant-BR, and among patients who are about to make a choice with respect to whether and which type of BR they would opt for. Special efforts should be made by plastic surgery associations to investigate and provide tools for guiding surgeons and patients in making well informed choices about BR.

However, please note breast conserving surgery must always be followed by radiotherapy and thereby is inevitably associated with adverse effects. As breast cancer survivors grow in number with increasing life expectancy, research on these adverse radiation effects becomes increasingly relevant to find strategies to reduce them and to improve our knowledge for patient counselling.

Conclusion

In conclusion, BCT is generally associated with fewer complications, similar QoL, and lower resource use, leading to superior cost-effectiveness compared to mastectomy followed by BR. We therefore believe that patients with breast cancer, for whom BCT is an oncologically safe alternative, should be counseled more towards this treatment (**chapter 6**). Large differences still exist between countries in the rates at which BCT and mastectomy are performed. For example, in Denmark the mean BCT rate is around 68% compared to around 59% in the Netherlands.[12] This suggests there is room for changes in treatment choices and counselling. An important challenge is educating breast cancer patients about the differences between treatments, with respect to survival, expected QoL, cosmetic outcomes, visits to the hospital and short- and long-term adverse effects of adjuvant treatments. No one-size-fits-all solution exists for this group of patients. Therefore, careful and preferably standardized exploration of the value the patient attributes to all aspects of her future treatment, its process and outcomes is warranted.

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Chapter 8

Nederlandse samenvatting

Waarom zouden we borstkanker patiënten meer borstsparende therapie moeten adviseren

In de gezondheidszorg zijn interventies er doorgaans op gericht het leven van de patiënt te verlengen en/of de kwaliteit van leven te verbeteren. Deze twee aspecten, een langere levensduur en een betere kwaliteit van leven, worden gecombineerd in de uitkomstmaat Quality Adjusted Life Years (QALY's).

Patiënten bij wie borstkanker is vastgesteld, zullen zich over het algemeen concentreren op het eerste doel: zij willen de kanker overleven. Na de diagnose bestaat de eerste keuze, die een patiënt met borstkanker en haar chirurg samen zullen moeten maken, uit een borstsparende operatie gevolgd door radiotherapie (borstsparende therapie, ofwel breast conserving therapy: BCT) of een borstamputatie (mastectomie). Indien zij kiezen voor een mastectomie, zal de patiënt voor een vervolgkeuze komen te staan: of en hoe zij haar borst wil laten reconstrueren.

In dit proefschrift werd onderzocht wat deze keuzes betekenen voor de patiënt, maar ook voor de samenleving, die de kosten draagt van de behandelkeuzen.

Kwaliteit van leven na borstkankerchirurgie

Eerdere studies hebben zich begrijpelijkerwijs hoofdzakelijk gericht op de gevolgen van de keuze voor één van deze chirurgische behandelingen op de levensverwachting van de patiënt. Uit meerdere betrouwbare studies is gebleken dat BCT geassocieerd is met een gelijke of zelfs iets gunstigere overleving bij patiënten met een vroeg stadium van borstkanker vergeleken met een mastectomie.[1-3] Omdat de overlevingsresultaten na mastectomie en BCT nagenoeg gelijk en tegelijkertijd relatief goed zijn,[1] wordt kwaliteit van leven na borstkankerbehandeling steeds belangrijker.

Er zijn veel meetinstrumenten ontwikkeld om op betrouwbare wijze de kwaliteit van leven van borstkankerpatiënten te kwantificeren, elk met zijn voor- en nadelen. Talrijke overheidsadviesorganen zoals NICE en ZiNL hebben echter gepropageerd dat als kwaliteit van leven wordt gebruikt om de waarde van verschillende behandelingen te vergelijken, de gebruikte meetinstrumenten in staat moeten zijn QALY's te berekenen. Verschillende instanties raden hiervoor het gebruik van de EQ-5D aan. De EQ-5D is een generieke gezondheidsgerelateerde kwaliteit van leven vragenlijst gebaseerd op de voorkeuren van de algemene Nederlandse bevolking voor specifieke gezondheidsuitkomsten. Het meetinstrument bestaat uit 5 items, die problemen met mobiliteit, zelfzorg, dagelijkse activiteiten, pijn/ongemak en angst/depressie meten.

De studie gepresenteerd in **hoofdstuk 2** laat zien dat een dergelijke, ogenschijnlijk eenvoudige uitkomstmaat, op betrouwbare en valide wijze kwaliteit van leven na borstkankerchirurgie evenals borstreconstructie (BR) kan meten.[4]

In een groot multicenter cross-sectioneel vragenlijstonderzoek (**hoofdstuk 3**) werd de kwaliteit van leven gemeten met de EQ-5D-5L bij patiënten na borstkanker. In de studie waren patiënten betrokken na BCT, alleen mastectomie, en mastectomie gevolgd door implantaat BR of autologe BR. De studie toonde de toegevoegde waarde aan van het sparen of reconstrueren van de borst boven alleen het uitvoeren van een mastectomie.[5] Er werden daarentegen geen statistisch significante verschillen in overkoepelende gezondheidsgerelateerde kwaliteit van leven uitkomsten gevonden tussen patiënten na BCT, implantaat BR en autologe BR. Postoperatieve complicaties hadden echter een grote en langdurige negatieve invloed op de kwaliteit van leven van patiënten, met name na autologe BR.

Kosteneffectiviteit van chirurgische behandeltrajecten van borstkanker

De zorgbudgetten staan zwaar onder druk door stijgende zorgkosten. De maatschappij, beleidsmakers en verzekeringsmaatschappijen staan daarom voor complexe keuzes over vragen als welke medische behandelingen in het basispakket van de zorgverzekeringen opgenomen moeten worden, welke behandelingen moeten blijven, en welke behandelingen plaats moeten maken. De kosteneffectiviteit van behandelingen is hierbij een belangrijk argument. Dit is niet alleen van belang bij de keuze tussen verschillende chirurgische behandelingen voor borstkanker, maar ook ten aanzien van de vraag wanneer de vergoeding van deze chirurgische behandelingen concurrerend is met andere toewijzingen van het zorgbudget. Dit is met name relevant voor veel voorkomende chirurgische behandeltrajecten voor borstkanker, zoals BR, omdat deze niet levensverlengend zijn, en waarbij de 'medische noodzaak' dus meer ter discussie staat.

Om deze reden is er een formele *'state-of-the-art'* kosten-batenanalyse uitgevoerd (**hoofdstuk 4**). Deze niet-gerandomiseerde, multicenter-cohort kosteneffectiviteitsanalyse geeft aan dat BCT het meest kosteneffectieve alternatief is, wanneer de borst gespaard of gereconstrueerd wordt.[6] Zowel implantaat BR als autologe BR waren aanzienlijk duurder dan BCT, met nauwelijks extra voordelen (QALY's). Dit maakt dat zij niet te bestempelen zijn als kosteneffectieve alternatieven boven BCT.

Als een borstreconstructie na mastectomie wordt overwogen, lijkt implantaat BR de meest kosteneffectieve techniek te zijn. Eén van de redenen voor de gunstigere kosteneffectiviteit van implantaat BR ten opzichte van autologe BR is dat de relatief vaak optredende complicaties van autologe BR een onevenredig grote invloed hebben op kwaliteit van leven en kosten. Dat blijft zelfs zo als er rekening gehouden wordt met heroperaties als gevolg van complicaties bij implantaten op de lange termijn, zoals implantaatruptuur of kapselcontractuur.

Er bestaan nog steeds grote verschillen tussen landen in de mate waarin BCT en mastectomie worden uitgevoerd. In Denemarken is bijvoorbeeld het gemiddelde aandeel BCT ongeveer 68% van alle chirurgische borstkankerbehandelingen. In Nederland is dat ongeveer 59%.[7] Dit suggereert dat er ruimte is voor veranderingen in de keuzes voor behandeling en voor counseling daarin.

De hogere kosten verbonden aan BR zijn niet alleen relevant vanuit een financieel perspectief. Zij zijn een rechtstreeks gevolg van langer durende operaties, meer ziekenhuisopnames en de noodzaak tot inzet van meer personeel; aspecten die alle op zichzelf van belang zijn wanneer de schaarse middelen in de gezondheidszorg op een verantwoorde wijze moeten worden verdeeld.

Een ontwikkeling op het gebied van BCT is de opkomst en ontwikkeling van oncoplastische chirurgie. Bij oncoplastische chirurgie bundelen oncologisch chirurgen en plastisch chirurgen hun krachten om de inzetbaarheid van borstsparende chirurgie uit te breiden, zodat grotere tumoren en tumoren met een ongunstige locatie verantwoord behandeld kunnen worden, wat anders zou hebben geleid tot ongunstige/ onaanvaardbare cosmetische resultaten.[8, 9] Er zullen verdere studies moeten worden uitgevoerd om te onderzoeken of de samenwerking inderdaad leidt tot een betere kwaliteit van leven en een goede kosteneffectiviteit van de behandeling.

Counseling van borstkankerpatiënten

Counseling van borstkankerpatiënten die een mastectomie moeten ondergaan is belangrijk. Het is in dit kader belangrijk om te beseffen dat BR geen levensreddende behandeling is, het wordt daarom ook wel ‘electieve chirurgie’ genoemd. Omdat BR als doel heeft de vorm van de borst te herstellen, zou het zelfs een cosmetische ingreep genoemd kunnen worden.

Omdat bij BR risico’s zijn verbonden aan de operatie en de waardering van een gereconstrueerde borst afhankelijk is van de patiënt, is de kwaliteit van het gesprek tussen chirurg en patiënt nog belangrijker, dan wanneer alleen risico’s moeten worden afgewogen tegenover zoiets evidents als een substantiële kans op overleven. In dat laatste geval is het voor de chirurg gemakkelijker om in de schoenen te staan van de patiënt. In het geval van een weging tussen de vorm van de borst en het risico op en de ernst van complicaties, is het echt een zaak van weging door de patiënt.

Zowel implantaat BR als autologe BR zijn geassocieerd met een relatief hoog risico op complicaties. Een recent groot prospectief onderzoek door Bennet et al. vond complicatiepercentages van ongeveer 26% voor implantaat BR (waarbij 15% een heroperatie nodig had) en ongeveer 47% voor autologe BR- technieken (waarbij 29% een heroperatie nodig had).[10] Dit zijn hoge risico’s voor deze electieve procedures.

De uitkomsten gepresenteerd in **hoofdstuk 3** toonden aan dat specifiek na autologe BR dergelijke complicaties geassocieerd zijn met een grote en langdurige negatieve invloed op de kwaliteit van leven.[5] Daarnaast liet het kwalitatieve onderzoek (**hoofdstuk 5**) zien dat als een complicatie leidt tot een totaal falen van de BR, dit gepaard gaat met een grote negatieve impact op zowel de patiënt als de chirurg.[11]

Belangrijke aspecten die naar voren kwamen (**hoofdstuk 5**) en waarmee rekening moet worden gehouden bij counseling van patiënten, zijn dat patiënten behandeld zouden willen worden met meer aandacht voor hun persoonlijke situatie, waarbij zij ook inzicht willen verkrijgen in de vraag welke invloed de chirurgische behandelingen op hun persoonlijke leven kunnen hebben, in plaats van een voorlichting vanuit een puur medisch-technisch perspectief.

Na een gefaalde BR kunnen de chirurgen schuldgevoelens ervaren die ook kunnen leiden tot een sterke drang om de mislukte BR te herstellen, terwijl patiënten juist minder geneigd zijn om aanvullende operaties te ondergaan. Daarnaast bleek dat de impact van het falen van een implantaat BR op een patiënt makkelijk kan worden onderschat door de chirurg. Voor patiënten met een gefaalde implantaat BR is dezelfde mate van intensieve nazorg en aandacht vereist als voor patiënten met een mislukte autologe BR.

De counseling van borstkankerpatiënten die een borstreconstructie wensen wordt verder nog gecompliceerd door een toenemend aantal studies die een groter risico laten zien dan eerder werd aangenomen op het ontwikkelen van de zeldzame en potentieel dodelijke aandoening anaplastisch grootcellig lymfoom (BIA- ALCL) voor vrouwen met een borstimplantaat.[12] Dit nieuws is op grote schaal door de media opgepikt en heeft in sommige landen geleid tot een verbod op bepaalde typen borstimplantaten. Dat heeft op zijn beurt geleid tot angst en veel vragen bij patiënten die eerder een implantaat BR hebben ondergaan en bij patiënten die op het punt staan een keuze te maken of en welk type BR zij zouden kiezen. Speciale inzet zou moeten worden geleverd door plastisch chirurgische beroepsverenigingen om een evidence-based hulpmiddel te ontwikkelen voor het begeleiden van chirurgen en patiënten bij het maken van goed gefundeerde keuzes over BR.

Tenslotte is het belangrijk zich te realiseren dat borstsparende operatie altijd wordt gevolgd door radiotherapie met de daarbij onvermijdelijke kans op lange-termijn-bijwerkingen. Het aantal overlevenden van borstkanker neemt toe evenals de levensverwachting, waardoor onderzoek naar de schadelijke lange-termijn-effecten van radiotherapie steeds belangrijker wordt om strategieën te ontwikkelen voor het verminderen van de risico’s en het verbeteren van onze voorlichting en begeleiding van borstkankerpatiënten.

Conclusie

Concluderend kan worden gesteld dat BCT geassocieerd is met:

- minder complicaties;
- een vergelijkbare kwaliteit van leven;
- geringer gebruik van zorgmiddelen.

Bovenstaande leidt tot een superieure (kosten-)effectiviteit in vergelijking met behandeling d.m.v. een borstamputatie al dan niet gevolgd door BR. Daarom is BCT een goed startpunt voor een consult over de mogelijke behandelopties aan patiënten met borstkanker (**hoofdstuk 6**).[13] In dit consult wordt voorlichting gegeven over: de verschillen tussen BCT en andere chirurgische behandelingen met betrekking tot de overleving, de verwachte kwaliteit van leven, cosmetische resultaten, bezoeken aan het ziekenhuis, mogelijke complicaties en de schadelijke effecten van aanvullende oncologische behandelingen zoals bestraling. Verder dient in dit consult ruimte te zijn voor bespreken van de waarde die de individuele patiënt hecht aan deze aspecten van haar behandeling, het proces en de uitkomst. Op basis hiervan kan in samenspraak de behandelkeuze worden gemaakt.

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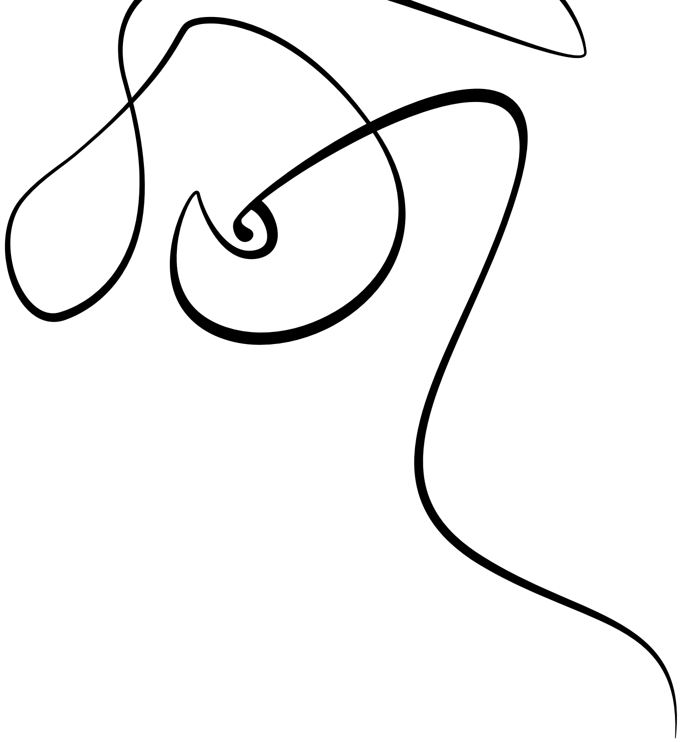

Appendices

PhD Portfolio

Name PhD student:	Casimir Alexis Eloi Kouwenberg
Erasmus MC department:	Plastic and reconstructive surgery *and* Psychiatry, Section Medical Psychology and Psychotherapy
Research School:	NIHES
PhD period:	Dec 2014-July 2020
Promotors:	Prof. dr. Marc A.M. Mureau *and* Prof. dr. Jan J. van Busschbach
Co-promotor:	Dr. Leonieke W. Kranenburg

1. PhD training

Courses			ECTS
05-02-2016	GW4588M	Advanced Research Methods	5.0
25-03-2015	GW4585M	Health Technology Assessment	5.0
26-01-2016	GW4567M	Economics and Financing of Health Care Systems	5.0
20-11-2015	GW4568M	Economics of Health and Health Care	5.0
14-02-2016	GW4570M	Health Care Governance	5.0
14-07-2016	GW4587M	Participating in HTA Research	5.0
26-08-2016	GW4580M	Patient Preferences in the Delivery of Health Care	5.0

Presentations, posters and abstracts

Presentations:

Fall meeting of the Netherlands Society for Plastic Surgery (NVPC), October 8^{th} 2016, Rotterdam, the Netherlands:

- "Is de standaard kwaliteit-van-leven uitkomstmaat in gezondheidseconomische evaluaties (EQ-5D) geschikt voor de evaluatie van borstreconstructie uitkomsten?"

Plastic Surgery The Meeting 2017, October 6 - 10, 2017 in Orlando, Florida

- "Propensity-Matched Analysis of Societal Preference-Based Quality of Life (EQ-5D): A Comparison of Both Autologous and Implant Breast Reconstruction with Mastectomy Only"

Fall meeting of the Netherlands Society for Plastic Surgery (NVPC), November 4^{th} 2017, Hengelo, the Netherlands:

- "Propensiteitscore gematchte analyse van maatschappelijke preferenties voor kwaliteit van leven (EQ-5D-5L): Een vergelijking van zowel autologe als protheseborstreconstructie met alleen mastectomie"

Fall Meeting Netherlands Society for Plastic Surgery (NVPC), November 3^{rd} 2018, Ede, the Netherlands:

- "Lange termijn kwaliteit van leven van vier chirurgische behandel opties voor borst kanker en de invloed van complicaties: een retrospectieve cohortstudie onder 1871 patiënten"
- "Beleving van patiënt en chirurg na het falen van een borstreconstructie: een kwalitatieve studie"

Posters:

San Antonio Breast Cancer Conference, 2018, San Antonio, Texas, USA

- "Long-term quality of life after four common surgical treatment options for breast cancer and the effect of complications – a retrospective patient-reported survey among 1871 patients"
- "Patients' and surgeons' experiences after failed breast reconstruction: a qualitative study"

Conference and seminars (attendance)

- Plastic Surgery The Meeting 2015, October 16-20, 2015 in Boston, Massachusetts, USA
- Fall meeting of the Netherlands Society for Plastic Surgery (NVPC), October 8^{th} 2016, Rotterdam, the Netherlands
- Plastic Surgery The Meeting 2017, October 6 - 10, 2017 in Orlando, Florida, USA
- Fall meeting of the Netherlands Society for Plastic Surgery (NVPC), November 4th 2017, Hengelo, the Netherlands
- Fall Meeting Netherlands Society for Plastic Surgery (NVPC), November 3^{rd} 2018, Ede, the Netherlands
- San Antonio Breast Cancer Conference, 2018, San Antonio, Texas, USA

2. Teaching Activities

	ECTS
Lecturing of clinical communication skills workgroups on the subjects: • Psychiatry • Gynecology • Surgery • Pediatrics	8.25
Coaching of 9 students in the first three years of medical school	2.0
Coaching during micro-surgical courses	2
Supervision of the master thesis of three medical students	6

Curriculum Vitae

Casimir Alexis Eloi Kouwenberg was born on 16th of March 1988, in Hilversum, the Netherlands. He attended secondary school in Hilversum, from which he graduated cum laude in 2006. In the same year he enrolled at University College Utrecht, the honors college of Utrecht University, where he followed the pre-medical school track with a minor psychology and neuroscience. During his bachelor's degree he spent one semester at University of California, Santa Barbara as part of an exchange program. He obtained his Bachelor of Science degree in 2009 (cum laude). In the same year he started the Selective Utrecht Medical Masters (SUMMA) program at Utrecht University, a Medical Doctor and Clinical Researcher master's program, during which he followed a minor Entrepreneurship and performed multiple medical internships abroad (Nicaragua, Curacao, Ecuador and the Palestinian territories). He did his research internship on the quality of life of patients with keloid disease, a combined project of the department of Plastic and Reconstructive Surgery and the department of Psychiatry section Medical Psychopathology under the supervision of dr. Eveline Bijlard, prof. dr. Marc Mureau, and prof. dr. Jan van Busschbach. After graduating he started his PhD project which was a collaboration of the same two departments. During his PhD project he attended and graduated from the Health Economics Policy and Law master's program of Erasmus University. In January 2020 he started his medical residency to become a psychiatrist at Parnassia Group in the Hague.

List of publications

Kouwenberg, C.A.E., Mureau, M.A.M., Kranenburg, L.W., Rakhorst, H., de Leeuw, D., Klem, T., Koppert, L.B., Ramos, I.C., Busschbach, J.J. Cost-utility analysis of four common surgical treatment pathways for breast cancer. Under Review. 2020.

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Dankwoord

Allereerst wil ik alle vrouwen die direct of indirect hebben deelgenomen aan de studies van dit proefschrift bedanken. Zonder jullie bijdrage was dit proefschrift nooit van de grond gekomen.

Prof. dr. S.E.R. Hovius, Ik wil u bedanken dat u in de hobbelige beginfase van het promotie-onderzoek onverminderd vertrouwen hield in een goede afloop. Ook zonder formele toewijzing van subsidiegeld gaf u groen licht en de daarvoor noodzakelijke financiële ondersteuning. Alsmede ben ik u dankbaar voor de bijdrage van de Esser stichting. Als laatste wil ik nog noemen uw ondersteuning van mijn aspiraties om de extra HEPL-master te volgen.

Prof. dr. M.A.M. Mureau, Beste Marc, Ik kan me de dag dat ik de voortgang van mijn masteronderzoek kwam bespreken bij jou op je kantoor in de Daniel den Hoed nog goed herinneren. Je gaf aan dat je tevreden was en benieuwd naar mijn plannen voor de toekomst. Al snel opperde je of ik niet interesse zou hebben een promotieonderzoek te doen. Een optie waarvan ik moet bekennen dat ik die nooit serieus had overwogen omdat schrijven nou niet echt mijn ding was. 6 jaar later is schrijven nog steeds niet echt mijn ding maar ben ik je wel dankbaar om mij binnen te hebben gehaald en voor alles wat ik op deze reis heb geleerd.

Prof. dr. J.J. van Busschbach, Beste Jan, Ik ben je uiterst dankbaar dat ik exact 6 jaar na onze eerste officiële meeting omtrent mijn promotieonderzoek dit onderzoek ook daadwerkelijk mag verdedigen. Op het moment ik overliep van nieuwe ideeën of verzandde in details was jij altijd bereid mij met je helikopterview weer op het juiste pad te brengen. Bedankt voor alle wijze lessen, hoofdzaak van bijzaak te leren scheiden, mij te adopteren op jouw afdeling "Medische Psychologie en Psychotherapie" en van de benodigde ondersteuning te voorzien.

Dr. L.W. Kranenburg, Beste Leonieke, Vaak vraag ik me af hoe ik de 969 dagen heb overleefd voor jij aan boord kwam bij het promotieonderzoek om mij op alle vlakken te inspireren en bij te staan. Ik ben je enorm dankbaar hiervoor.

Dr. H. Rakhorst, Beste Hinne, Bedankt voor je inzet. Jouw gave en inzicht om verbindingen te leggen hebben het mogelijk gemaakt ons onderzoek naar een breder vlak te trekken.

Geachte leden van de promotiecommissie, ik wil u hartelijk bedanken voor jullie bereidheid mijn proefschrift te beoordelen en zitting te nemen in de promotiecommissie.

Evelien en Xavier, Daar waar het allemaal begon met het onderzoek bij de Plastische Chirurgie en zonder wiens inspiratie ik dit pad nooit was ingeslagen. Bedankt voor jullie steun en inzichten als spar-, onderzoekspartners en vrienden.

Staf, assistenten en onderzoekers van de Plastische Chirurgie en dames van het skills-lab bedankt voor het mooie pad dat we samen hebben bewandeld. Ondanks dat onze wegen hierna andere kanten opgaan zal ik altijd met een warm gevoel terugkijken op deze periode.

Collega's van de Medische Psychologie en Psychotherapie bedankt voor jullie warme welkom op de afdeling. Het met mij delen van kennis op het gebied van onderzoek en onderwijs en alle mooie ervaringen. Ik heb buitengewoon veel van jullie geleerd. Lothar, Martijn, Sohal en Steef wat was het een ellendige bedoening geweest als ik zonder ons relativerende gebral op onze kamer en later bij Ari's die 6 jaar door had moeten komen. Bedankt mannen! Wietske bedankt voor je inspirerende en tomeloze positieve energie, rust in vrede. Hetty en Maya bedankt voor de gezellige pitstops bij het secretariaat. Reinier voor je geduldige assistentie.

Artikelen schrijven doe je zelden alleen en zonder de hulp van mijn geweldige coauteurs had het boekje er nu niet gelegen. In het bijzonder wil ik bedanken Isaac, Kelly, Lothar, Martijn en Sohal.

Beste Jan Dirk en Wijbrand bedankt voor het mogelijk maken mijn onderzoek tijdens mijn opleiding psychiatrie voorspoedig af te ronden zonder dat mijn kwaliteit van leven te veel heeft moeten inleveren.

Jessica Gopie, Aad Tibben en Mirjam Hoefkens, bedankt voor jullie samenwerking, het delen van jullie data van het begin van het mooie interessante onderzoek naar de ervaringen van patiënten en chirurgen na het falen van een borst reconstructie. En de mogelijkheid deze alsnog tot een artikel te verwerken.

Last but definetly not least, alle vrienden, familie en oud-huisgenoten met wie ik gelukkig, in de tijd dat ik niet met data zat te zwoegen, prachtige tijden heb kunnen beleven tijdens mijn promotieonderzoek. Bedankt voor het geven van licht en leven in de soms donkere tijden van het onderzoeksleven!